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Original Communications

EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

III. EFFECTS ON THE CORONARY BLOOD FLOW*

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THE object of this investigation was to ascertain the effect of therapeutic and toxic doses of digitalis on the coronary blood flow in the intact, trained animal.

LITERATURE

Numerous observations have been made on the effect of digitalis on the extracardiac vessels. Fothergill,[1] Klug,[2] and Donaldson and Stevens[3] stated that digitalis constricted the small vessels in the web of the frog's foot; Legroux[4] and Boehm,[5] on the contrary, did not observe any change in the vessels after the administration of digitalis. Legroux, Gourvat,[6] Klug, and Kraft[7] described constriction of the blood vessels in the ear of the rabbit; Koppe[8] stated that the vessels were dilated by digitalis bodies. Ackermann[9] and Gourvat observed constriction of the mesenteric vessels after the administration of digitalis. Boek[10] reported vasoconstriction in the isolated limbs of dogs after the vessels had been perfused with strophanthin. Jonescu and Loewi[11] studied the renal vessels plethysmographically, and observed that digitalis may cause vasodilatation; Joseph,[12] on the contrary, described vasoconstriction in the renal vessels. Eppinger and Hess[13] and Cow[14] observed constriction of isolated rings of peripheral blood vessels after the administration of digitalis; Rabe[15] found no change or slight constriction in isolated strips of arteries.

Likewise, many studies have been made on the cardiac vessels before and after the administration of digitalis or of allied substances. Eppinger and Hess found that digitoxin, digalen, and strophanthin de-

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creased the caliber of rings of coronary artery. Rabe observed constriction of rings of coronary artery. Cow described dilatation of rings of coronary artery after the administration of digitalin. Voegtlin and Macht[16] stated that isolated rings of coronary artery were constricted by digitalin (Merck) and digitoxin (Merck), dilated by digalen, slightly constricted by digitalin (Kiliani), and unchanged by strophanthin (Merck) and strophanthin (Boehringer). Bond[17] and Meyer[18] studied the volume outflow from severed and cannulated superficial coronary veins. Meyer observed that digalen, g-strophanthin, digipuratum soluble, and digistrophan increased the flow, whereas Bond concluded that digitalis and strophanthin did not produce any change in the flow. Gunn[19] did not observe any change in coronary blood flow after the administration of strophanthin; he used the isolated heart of the rabbit and the Condon recorder to measure the flow.

Most of the measurements of coronary blood flow have been made by inserting a Morawitz cannula in the coronary sinus. Sakai and Saneyoshi[20] concluded that strophanthin in large doses causes vasoconstriction, whereas, in doses approximating those employed clinically, the drug produces little or no change in the blood flow. Bodo[21] observed an increase in coronary blood flow after the administration of large doses of tincture of digitalis (10 c.c. to a heart-lung preparation within twenty-six minutes), and also after the administration of 0.3 mg. of strophanthin. Fisher, Guggenheimer, and Müller[22] observed a decrease in coronary flow after the administration of strophanthin (0.2 mg., for example). Gilbert and Fenn[23] concluded that ouabain, digitoxin, and tincture of digitalis (even 20 to 30 per cent of the minimal lethal dose) decreased the coronary flow by vasoconstriction. Rühl and Wiehler[24] likewise observed vasoconstriction after the administration of strophanthin. Ginsberg, Stoland, and Siler[25] found that the administration of digitalis in the Starling preparation decreased the coronary flow for ten minutes, and then increased it.

The thermostromuhr method of Rein[26] has been used in recent years to study the coronary blood flow. Hochrein[27] stated that digitalis (0.4 c.c. of digipurat) increased the coronary blood flow in some animals and decreased it in others. Essex, Herrick, Baldes, and Mann[28] gave approximately 30 per cent of the minimal lethal dose of digiglusin to trained, unanesthetized dogs, and did not observe any significant changes in coronary blood flow as measured by the Baldes-Herrick[29] modification of the Rein thermostromuhr. The coronary blood flow was measured daily for a period as long as nine days. Essex, Herrick, and Visscher[30] injected solutions containing lanatoside A, B, and C (subnauseating doses, varying from 10 to 20 per cent of the minimal lethal dose) into trained, unanesthetized dogs. With the thermostromuhr method, the coronary blood flow was unchanged. Hildebrandt and Osterwald,[31] using the Rein thermostromuhr, did not observe any change in coronary flow after 0.15 to 0.5 mg. of strophanthin per kilo-

gram had been administered to dogs anesthetized with morphine and pernocton. This dosage was estimated to be within the therapeutic range; toxic doses caused a decrease of the coronary blood flow, then an increase.

In a critical evaluation of the foregoing experimental methods of measuring coronary blood flow after the administration of digitalis, the following factors deserve comment. The isolated ring method is obviously very unphysiologic. The volume of flow from a severed superficial coronary vein is not a reliable index to the flow of blood in the coronary arteries; too many factors may change the venous flow, with or without a corresponding change of flow in the coronary arteries. The coronary blood flow in the heart-lung preparation may be altered by the effects of the preparatory operative procedure, by the anesthetic agent, and by the fact that the heart usually is denervated.

It must be borne in mind that these experimental methods are adapted to measuring coronary blood flow over periods varying from a few minutes to several hours. They do not permit one to follow the volume of flow over long periods after digitalis has been administered. Furthermore, estimation of the dose of digitalis which would correspond to that ordinarily used in an intact animal or in man is difficult in these experimental preparations.

The thermostromuhr measurements of the coronary blood flow are the only ones which produce values that can be assumed to approach physiologic limits. The trained animals are intact. Their coronary blood flow may be measured at any time during a control period of several days, and at any time over a period of days after the digitalis has been given.

METHODS

In the experiments on blood flow, dogs were used because these animals have coronary arteries which are large enough to permit the application of the thermostromuhr unit.

Fourteen dogs were prepared for these experiments, six of which were satisfactory for observations on the coronary blood flow. Seven animals were unsatisfactory for the following reasons: development of postoperative complications (three dogs), occlusion of the vessels under the thermostromuhr unit (one dog), malfunction of the unit (one dog), a break in the lead wires from the unit within the animal's thorax (one dog), and disjunction of the unit and the coronary artery, so that the former lay free in the thoracic cavity (one dog). One animal which did not have a unit applied to the coronary artery was used for measurements of blood pressure before and after the administration of a toxic dose of digitalis.

The sequence of experimental procedures used to obtain the coronary blood flow readings may be summarized briefly:

1. Each animal was trained to lie quietly on its right side on a table. Several days were required to train the average dog.

2. The Rein thermostromuhr unit (as modified by Baldes and Herrick) was applied to the circumflex branch of the left coronary artery while the animal was under general anesthesia and was connected with an artificial respirator. Sterile operative technique was used to expose the heart through an incision between the fifth and sixth ribs on the left side. A short segment of the previously mentioned coronary artery was carefully dissected free from the adjacent tissue. A thermostromuhr unit of the proper size was fastened to this isolated portion of the coronary

artery. In addition, the lead wires from the unit were sutured to the epicardium to aid in stabilizing the unit on the coronary artery. The pericardium and the chest wall were then closed with sutures. The lead wires from the unit were permitted to emerge from the anterior (ventral) portion of the incision.

3. After the animal had recovered sufficiently from the immediate effects of the operation (twenty-four to forty-eight hours), had attained its approximately normal body temperature, had regained its appetite, and had been able to run about the laboratory without any apparent discomfort or illness, daily measurements of the coronary blood flow were made. Before the reading of the blood flow was made each day, the animal was made to lie quietly on a table for thirty minutes to one hour in order to obtain, as nearly as possible, a basal value for the coronary blood flow.

4. When the daily measurements of the coronary blood flow remained fairly constant, the appropriate dose of digitalis was injected intravenously. The intravenous route was chosen in order to make certain that all of the drug, in any given dose, entered the circulation.

5. After the digitalis had been administered, daily measurements of the coronary blood flow were made. (Each animal was made to lie quietly on the table until a sustained basal flow reading was obtained.) In some of the animals, measurements of blood flow were made at intervals of one hour during the first six to eight hours after the drug had been injected. Nausea and vomiting, however, limited the value of these immediate readings.

6. The experiment was terminated when the lead wires broke within the thoracic cavity, or when the animal was killed in order to study the myocardium grossly and microscopically.

In selecting the animals, an endeavor was made to use old dogs. It had already been shown[32] that old cats are more sensitive to digitalis than young ones.

The animals were fed daily after the blood flow had been measured.

The construction of the thermostromuhr unit and its calibration have been described by Rein, Baldes and Herrick, and Herrick and Baldes,[33] and the description need not be repeated here.

Measurements of blood pressure were made on some of the animals with the manometer technique of Hamilton, Brewer, and Brotman.[34]

The digitalis preparations which we used were as follows: (1) digifoline, 2 c.c. = 1 cat unit; (2) digalen, 2 c.c. = 1 cat unit; (3) digitoxin, 0.575 mg. per kilogram of dog = minimal lethal dose; (4) lanatoside A, 0.437 mg. per kilogram of dog = minimal lethal dose.

It was estimated that 30 per cent of the minimal lethal dose was equivalent to the "calculated therapeutic dose." Eighty per cent of the minimal lethal dose was definitely toxic. It has been shown[32] that 80 per cent of the minimal lethal dose of digitalis may produce histologic changes in the heart of the cat. The lethal dose of digitalis for the dog was taken to be approximately 25 per cent greater than that for the cat.

RESULTS

Care was taken to use only those animals which had recovered from the operative procedure and were, to all intents and purposes, in good condition. An endeavor was made to keep the animal as quiet as possible when the measurements of average minimal blood flow were made each day.

A. Effects of Calculated Therapeutic Doses of Digitalis on the Coronary Blood Flow.—In confirmation of the work of Essex, Herrick, Baldes, and Mann,[28] the estimated therapeutic dose of digitalis (30 per

cent of the minimal lethal dose of digalen) did not produce any significant change in blood flow in the circumflex branch of the left coronary artery over a period of three days (Fig. 1 and Table I). There was no significant change in coronary blood flow after the administration of 30 per cent of the minimal lethal dose of digitoxin over a period of three days (Fig. 2).

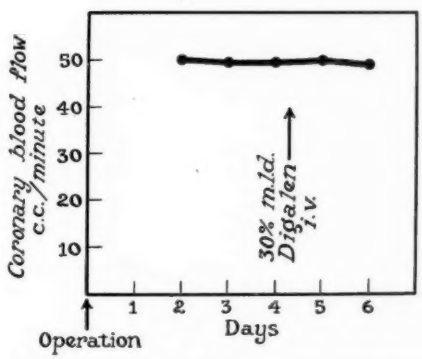

Fig. 1.—No change in coronary blood flow after intravenous administration of calculated therapeutic dose of digitalis (30 per cent of minimal lethal dose of digalen). No histologic changes were found in the myocardium of this animal.

TABLE I

CORONARY BLOOD FLOW OF A 15-KILOGRAM DOG AFTER THE INJECTION OF A CALCULATED THERAPEUTIC DOSE OF DIGITALIS (30 PER CENT OF MINIMAL LETHAL DOSE OF DIGALEN)

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	AVERAGE BLOOD FLOW, C.C. PER MINUTE	TIME OBSERVED AFTER OPERATION	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPERATURE, DEGREES F.	REMARKS
	50.2	48 hr. (2 days)	130	103.2	
	49.7	72 hr. (3 days)	132	103.0	
	49.4	96 hr. (4 days)	108		Animal's condition satisfactory
30% digalen		103 hr.			
	50	120 hr. (5 days)			Note no change of rate of flow with calculated therapeutic dose
	49	144 hr. (6 days)	100	102	Mechanical break in lead wires
		168 hr.			

B. Effects of Toxic Doses of Digitalis on the Coronary Blood Flow.—Fig. 2 and Table II indicate that, although a calculated therapeutic dose of digitalis (30 per cent of the minimal lethal dose of digitoxin) did not change the coronary blood flow, a toxic amount of the drug (63 per cent of the minimal lethal dose of digitoxin) decreased the volume of flow from 96 to 61 c.c. per minute. The decrease of blood

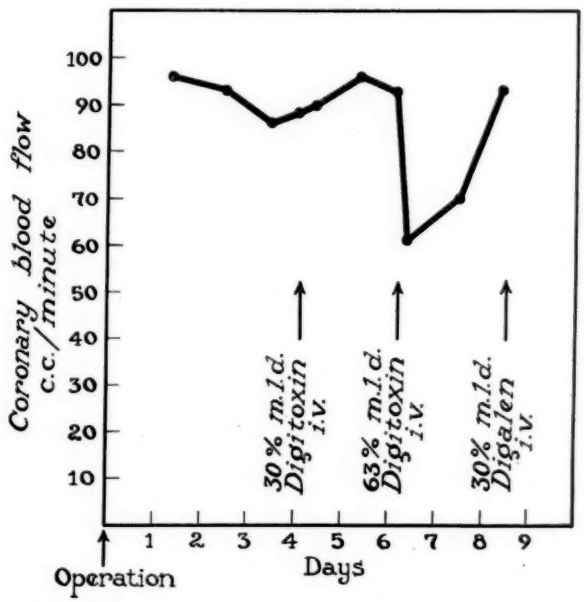

Fig. 2.—No significant change in coronary blood flow after intravenous administration of calculated therapeutic dose of digitalis (30 per cent of minimal lethal dose of digitoxin). Decrease of coronary blood flow after intravenous administration of toxic dose of digitalis (63 per cent of minimal lethal dose of digitoxin); the diminution of coronary blood flow was not sustained. The animal died promptly after injection of third dose of drug. No myocardial lesions were found.

TABLE II

CORONARY BLOOD FLOW OF A 26-KILOGRAM DOG AFTER THE INJECTION OF A THERAPEUTIC DOSE OF DIGITALIS (30 PER CENT OF MINIMAL LETHAL DOSE OF DIGITOXIN) AND AFTER INJECTION OF TOXIC DOSE OF DIGITALIS (63 PER CENT OF MINIMAL LETHAL DOSE OF DIGITOXIN)

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	AVERAGE BLOOD FLOW, C.C. PER MINUTE	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPERATURE, DEGREES F.	TIME OBSERVED AFTER OPERATION	REMARKS
	96	126	102.8	32 hr. (1 day+)	
	93	126	101.6	59 hr. (2 days+)	Excellent condition. Average control flow 90.6 c.c.
	86	100	101.6	82 hr. (3 days+)	
	88	106	101.6	97 hr. (4 days+)	
30% digitoxin					
	90	72	101.4	106 hr.	8 hr. after digitoxin; no decrease flow
	96	126	101.8	128 hr. (5 days+)	
63% digitoxin					
	61	68	101.4	152 hr. (6 days+)	Numerous premature contractions
	70	66		179 hr. (7th day)	Numerous premature contractions
	93	156	102	203 hr. (8th day)	Regular, but rapid, pulse. Dog was given 30% of minimal lethal dose of digalen intravenously. Died promptly

flow was not sustained; forty-eight hours after the toxic dose had been injected, the blood flow had returned to its previous level, i.e., 93 c.c. per minute. A third injection of 30 per cent of the minimal lethal dose of digalen caused the animal to die within a few hours. No histologic changes were observed in the heart of this animal.

Table III shows a marked increase in coronary blood flow during the stage of nausea. The blood flow increased from 160 to 285 c.c. per

TABLE III

CORONARY BLOOD FLOW OF AN 18.4 KILOGRAM DOG AFTER THE INJECTION OF A TOXIC DOSE OF DIGITALIS (80 PER CENT OF MINIMAL LETHAL DOSE OF DIGALEN)

Note rise of coronary blood flow in stage of nausea and fall of blood flow in postnausea stage

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	TIME OBSERVED AFTER OPERATION	AVERAGE BLOOD FLOW, C.C. PER MINUTE	PULSE RATE, BEATS PER MINUTE	BLOOD PRESSURE, MM. HG	RECTAL TEMPERATURE, DEGREES F.	REMARKS
	48 hr. (2nd day)	168	86		101.8	
	82 hr. (3rd day)	155	90	198/112	101.8	Average control flow, 162.7 c.c. per minute
	88 hr. (3rd day)	165	86			
	96 hr. (4th day)	163.5	78		101.8	
	101 hr. (4th day)	160	78		101.6	
80% digalen	4th day	160	64			Restless; uncomfortable
	½ hr. after injection					Restless; nauseated, emesis
	1 hr. after injection	285				Nausea and vomiting
	2 hr. after injetcion	235	138			No emesis past hr. Restless
	3 hr. after injection	172	124			Extrasystoles. Emesis within hr. Quiet
	4 hr. after injection	140	100			Quiet
	8 hr. after injection	105	120			Maximal decrease of flow recorded
	132 hr. (5th day)	144	94		101.4	Extrasystoles. Dog restless. Not basal value
	156 hr. (6th day)	128	96	202/117	101.2	Quiet
	179 hr. (7th day)	134	78		101.3	Extrasystoles. Quiet
	190 hr. (8th day)	132	74		101.2	Dog quiet. Lead wires to unit broken inside chest. Dog recovered

minute one hour after the administration of a toxic dose of digitalis (80 per cent of minimal lethal dose of digalen). Eight hours after the

TABLE IV

DECREASE IN CORONARY BLOOD FLOW IN A 13.3-KILOGRAM DOG

Decrease was maintained over a period of days by repeated doses of digitalis in the toxic range

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	TIME OBSERVED AFTER OPERATION	AVERAGE BLOOD FLOW, C.C. PER MINUTE	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPERATURE, DEGREES F.	REMARKS
	23 hr.	51.2			
	31 hr.	52.5	130	104	Condition fair (average control flow, 52.3 c.c. per minute)
	48 hr. (2 days)	51.6	120	103.2	
	72 hr. (3 days)	54	120	102.4	
80% digitoxin	73 hr.		32		Pulse rate 32, 20 minutes after injection
	78 hr.	38	102	102.4	6 hr. after injection of digitoxin
	96 hr. (4 days)	36	66	102.4	24 hr. after injection of digitoxin. Bigeminal pulse
	120 hr. (5 days)	34.6	82		48 hr. after injection of digitoxin. Extrasystoles
	144 hr. (6 days)	32.6	70	102.4	74 hr. after injection of digitoxin. Regular pulse
	168 hr. (7 days)	38	78	103.1	96 hr. after injection of digitoxin. Animal seems in good condition
	192 hr. (8 days)	38	80	102.6	120 hr. after injection of digitoxin
	216 hr. (9 days)	36	66		
30% digitoxin	217 hr.				
	224 hr. (9 days)	32.6	66	102.2	24 hr. after 2nd injection digitoxin
	240 hr. (10 days)	33		103.2	48 hr. after 2nd injection digitoxin
	264 hr. (11 days)	29.5	64	102.4	72 hr. after 2nd injection digitoxin
40% digitoxin	265 hr.				
	288 hr. (12 days)	36.8	128		Note rapid rate heart
	312 hr. (13 days)	27	64	101.8	Maximal decrease of flow 48%
	336 hr. (14 days)	27.2	64	102.2	Extrasystoles. Dog seems in good condition
	384 hr.	30.5	72	102.2	Dog killed to study myocardium microscopically

drug had been injected the coronary blood flow was decreased to 105 c.c. per minute. During the next four days the flow rose gradually to 132 c.c. per minute. The experiment was terminated when the wires to the thermostromuhr unit were broken within the thoracic cavity of the animal. The unit was removed from the coronary artery and the animal recovered completely.

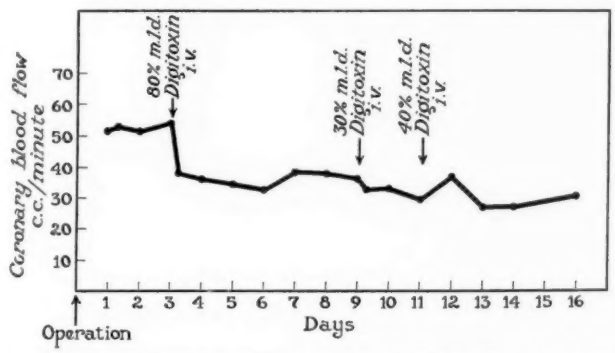

Fig. 3.—Decrease in coronary blood flow after administration of toxic doses of digitalis. The doses of digitalis bodies were spaced in an endeavor to maintain the coronary blood flow below the control level. Histologic changes were found in the myocardium.

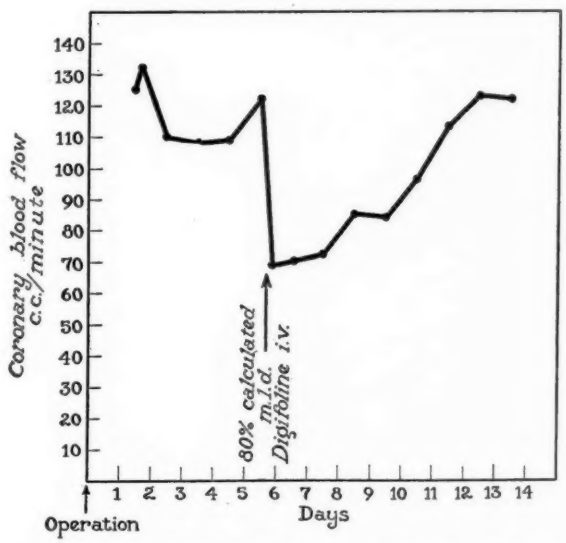

Fig. 4.—Decrease in coronary blood flow after administration of a single toxic dose of digitalis. Note that the coronary blood flow returned to the preinjection levels. The animal recovered completely.

Fig. 3 and Table IV also show a decrease in coronary blood flow after the administration of toxic doses of digitalis (digitoxin). In this experiment, an endeavor was made to maintain the coronary blood flow below the control level for a prolonged period (fourteen days). Fig. 3 is self-explanatory. The animal was killed in an ether chamber on

the sixteenth day of the experiment so that the myocardium might be studied microscopically. Histologic changes were observed in the left ventricular wall and in the interventricular septum. These anatomic changes were similar to those described in the first paper of this series.[32] There was no evidence of occlusion of the coronary artery, either directly within the unit or elsewhere along the course of the vessel.

In order to make more certain that the decrease of coronary blood flow was not caused by intravascular thrombosis within the thermo-

TABLE V

DECREASE IN CORONARY BLOOD FLOW AFTER THE INJECTION OF A TOXIC DOSE OF DIGITALIS; RETURN OF FLOW TO THE APPROXIMATE CONTROL LEVEL AFTER A PERIOD OF DAYS

DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	TIME OBSERVED AFTER OPERATION	AVERAGE BLOOD FLOW, C.C. PER MINUTE	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPERATURE, DEGREES F.	REMARKS
	24 hr. (1 day)	175	106	102.2	Restless. Not basal
	48 hr. (2 days)	100	98	102.2	
	72 hr. (3 days)	120	80	102.2	Average = 113 c.c. per minute
	96 hr. (4 days)	120	84	102.4	
	120 hr. (5 days)	112	48	102.0	
	128 hr.	113	54		
80% lanatoside A	144 hr. (6 days)	88.5	88	100.0	Vomited in morning 14 hr. after injection of lanatoside A
	168 hr. (7 days)	101	72	101.6	Restless—not basal flow.
	192 hr. (8 days)	68	46	101.0	Pulse regular
	216 hr. (9 days)	72	46	101.6	Bigeminal pulse
	240 hr. (10 days)	72	58	101.2	Bigeminal pulse
	264 hr. (11 days)	90	49	101.6	Regular pulse. Restless
	288 hr. (12 days)	82			Animal in good condition
	312 hr. (13 days)	96	50	101.1	
	360 hr. (15 days)	100	66		Pulse irregular (extrasystoles)
	384 hr. (16 days)	100.1	66		Pulse irregular (extrasystoles)
	17 days				Wires broken to heater and thermocouple. Unit removed from vessel 20 days after operation. Vessel patent. Animal recovered; wound healed in few days

stromuhr unit, two old animals were given single toxic doses of digitalis, after which the measurements of blood flow were made daily until the values reached the preinjection readings. Fig. 4 and Tables V and VI give the results of these two experiments. Both animals recovered completely. No evidence of intravascular thrombosis was noted within the units when the latter were removed from the coronary vessels.

Our data do not permit a definite explanation for the behavior of the coronary blood flow in these two experiments.

C. Observations on Blood Pressure, Pulse Rate, and Coronary Blood Flow After the Administration of Toxic Doses of Digitalis.—No definite

TABLE VI

DECREASE IN CORONARY BLOOD FLOW OF A 15-KILOGRAM DOG AFTER THE INJECTION OF A TOXIC DOSE OF DIGITALIS; RETURN OF CORONARY BLOOD FLOW TO THE PREINJECTION LEVEL AFTER A PERIOD OF DAYS

Blood pressure and pulse rate are recorded

OP. 9/25/40 10:30 A.M.	DRUG GIVEN INTRAVENOUSLY, PER CENT OF MINIMAL LETHAL DOSE	AVERAGE BLOOD FLOW, C.C. PER MINUTE	BLOOD PRESSURE, MM. HG	PULSE RATE, BEATS PER MINUTE	RECTAL TEMPERATURE, DEGREES F.	REMARKS
9/26/40 10:30 a.m.		128		108	103.0	Animal restless
9/27/40		110		98	103.4	
9/28/40 12:00 m.		108		76	102.2	Animal quiet
9/29/40 2:30 p.m		108		82	102.4	Restless
9/30/40 12:00 m.	80% digifoline	122	223/110	82	102.2	Restless
9/30/40		69		80	102.2	
10/ 1/40 1:30 p.m.		70	157/100	132	101.8	Quiet
10/ 2/40 2:00 p.m.		72	187/102	62	101.8	
10/ 3/40 2:00 p.m.		85	204/100	76		
10/ 4/40 2:00 p.m.		84	192/99	66	102.0	Animal in excellent health
10/ 5/40 2:00 p.m.		96		72	101.8	
10/ 6/40 2:00 p.m.		113		68	102.0	
10/ 7/40 2:00 p.m.		123		76		
10/ 8/40 2:00 p.m.		122	215/104	70		Animal quiet; recovered
10/15/40			225/117	123		
10/22/40			205/117	147		
10/30/40	80% digifoline					
10/31/40			138/92	147		
11/ 1/40			206/95	57		
11/ 2/40			191/104	93		
11/ 4/40			226/112	63		

correlation could be established between the blood pressure or pulse rate and the decrease of coronary blood flow after the administration of toxic doses of digitalis to trained dogs.

Table III shows that the blood pressure two days after injection of a toxic dose of digitalis (80 per cent of the minimal lethal dose of digalen) was approximately the same as the control reading although the coronary blood flow had not yet returned to the preinjection value. The pulse rate during the preinjection recording of blood pressure was approximately the same as it was two days after the toxic dose of digitalis had been administered.

In one case there was a lack of significant change in blood pressure two days after a toxic dose of digitalis (80 per cent of minimal lethal dose of digalen) had been administered. The blood pressure before injection was 228/128 (pulse rate = 132 per minute); two days after the injection it was 214/121 (pulse rate = 96 per minute). Measurements of coronary blood flow were not made in this case.

Table II shows that there was a decrease of pulse rate after the injection of a calculated therapeutic dose of digitalis (30 per cent of the minimal lethal dose of digitoxin), but no further decline of pulse rate occurred when a toxic dose of digitalis (63 per cent of the minimal lethal dose of digitoxin) was administered to the animal. The blood pressure was 171/98 the day before the toxic dose was given, and 178/93 the day after the toxic dose had been administered. Although the blood pressure did not change significantly, the coronary blood flow was decreased from 96 to 61 c.c. per minute on the day these measurements of blood pressure were made. In this experiment the pulse rate fell from 126 to 66 per minute.

Table VI shows a decrease of blood pressure on two occasions after toxic doses of digitalis had been given. On the first occasion the blood pressure was 223/110, and coronary blood flow, 122 c.c. per minute, before the digitalis was administered. The day after the injection of 80 per cent of the minimal lethal dose of digifoline the blood pressure fell to 157/100, and the coronary blood flow was decreased to 70 c.c. per minute. The change in blood pressure was primarily in the systolic level; the change in the diastolic pressure was not very significant. On the second occasion the fall of blood pressure was more striking. A month was permitted to elapse between the first and the second injection of digitalis. The blood pressure was 205/117 (pulse rate = 147 per minute) before the second injection of 80 per cent of the minimal lethal dose of digifoline; the pressure fell to 138/92 (pulse rate = 147 per minute) the day after the administration of the drug.

A series of control readings of blood pressure were made on an animal over a period of seventeen days (Table VII); then a toxic dose of digitalis (80 per cent of the minimal lethal dose of digifoline) was injected intravenously. No significant change in the blood pressure was observed during the next thirty days. The pulse rate values are also recorded in Table VII.

TABLE VII

BLOOD PRESSURE AND PULSE RATE BEFORE AND AFTER THE INJECTION OF A TOXIC DOSE OF DIGITALIS

DATE OBSERVED	BLOOD PRESSURE, MM. HG	PULSE RATE, BEATS PER MINUTE	BODY TEMPERATURE, DEGREES F.
9/18/40	219/104	104	102.6
9/20/40	215/105	105	101.2
9/23/40	209/116	124	101.8
9/25/40	225/109	105	102.0
9/27/40	213/116	105	101.2
10/ 2/40	222/109	108	101.8
10/ 5/40	221/114	129	102.0
10/ 7/40	80% of minimal lethal dose of digifoline intravenously		
10/ 8/40	229/110	96	101.0
10/10/40	231/117	90	101.8
10/15/40	209/124	150	101.6
10/22/40	184/100	148	101.6
10/31/40	206/96	96	102.0
11/ 7/40	204/100	117	101.2
11/12/40	247/109	114	102.0
11/20/40	204/116	111	101.8
11/27/40	214/103	102	102.0
12/ 4/40	209/103	102	101.0
12/ 9/40	220/103	93	101.2

COMMENT

One of the most likely sources of error in these experiments is in estimating the dose of digitalis for the dog which will correspond to any given dose of the drug in man. It is to be remembered that the dog is less sensitive to digitalis than the cat, and probably also is less sensitive to the drug than man. For the lack of a better method, we have expressed the quantity of digitalis in terms of the minimal lethal dose for the dog. Sources of error in the technical procedure involved in the thermostromuhr method of measuring coronary blood flow were minimized as much as possible. The units were selected and calibrated carefully. They were applied snugly to the coronary artery and anchored securely to avoid compression of the vessel.

Control readings were made after the animals had recovered from the immediate effects of the operation and were observed to be free from significant postoperative complications. The body temperature and the cardiac rate were recorded in all cases. Estimations of blood pressure were made in some cases in order to ascertain whether variations in systemic pressure might be contributing to the changes in coronary blood flow.

The individual measurements of the coronary blood flow were often checked by independent observers and the results compared.

Care was taken to have the animal in as nearly a basal state as possible before each final measurement of the coronary blood flow was made each day. If the animal was restless, the measurements of coronary blood flow were variable and unsatisfactory.

We wish to avoid an error in the interpretation of our experiments

by stating that we are uncertain of the mechanism by which the coronary blood flow is decreased by toxic doses of digitalis or is maintained at a level below the control readings for periods of days.

SUMMARY

Calculated therapeutic doses of digitalis did not produce a significant change in the coronary blood flow of the dog. This confirms the results of Essex, Herrick, Baldes, and Mann.[28]

Calculated toxic doses of digitalis decreased the coronary blood flow of dogs four to six hours after the drug had been administered. The diminution of flow persisted for several days after a single toxic dose of the drug.

No myocardial lesions were observed after a therapeutic dose of digitalis, nor were they observed in one animal which received a toxic dose of digitalis. In the latter animal the coronary blood flow returned to the preinjection level within two days.

Myocardial lesions were observed in one animal in which the coronary blood flow was kept well below the control level for twelve days by repeated injections of digitalis (toxic range).

The diminution of coronary blood flow after the injection of toxic doses of digitalis could not be correlated consistently with changes in the pulse rate or systemic blood pressure.

After the injection of toxic doses of digitalis the coronary blood flow returned to the control level in several experiments, and the animals recovered completely.

REFERENCES

1. Fothergill, J. M.: On Digitalis: Its Mode of Action and Its Use, Brit. M. J. **2**: 5, 27, 1871.
2. Klug, Ferdinand: Ueber die Wirkung des Digitalins auf die Blutgefässe und das Herz, Arch. f. Anat. u. Physiol., p. 457, 1880.
3. Donaldson, H. H., and Stevens, L. T.: The Influence of Digitaline on the Work of the Heart and on the Flow Through the Blood-Vessels, J. Physiol. **4**: 165, 1882-1883.
4. Legroux: Quoted by Cushny, A. R.: The Action and Uses in Medicine of Digitalis and Its Allies, New York, 1925, Longmans, Green and Co.
5. Boehm, Rudolf: Untersuchungen über die physiologische Wirkung der Digitalis und des Digitalin, Pflüger's Arch. f. d. ges. Physiol. **5**: 153, 1872.
6. Gourvat: Quoted by Cushny, A. R.: The Action and Uses in Medicine of Digitalis and Its Allies, New York, 1925, Longmans, Green and Co.
7. Kraft, I.: Einfluss der Herzmittel auf den Rhythmus der peripheren Gefässe, Pflüger's Arch. f. d. ges. Physiol. **204**: 491, 1924.
8. Koppe, Robert: Arbeiten aus dem Institut für experimentelle Pharmakologie zu Strassburg. 8. Untersuchungen über die pharmakologischen Wirkungen des Digitoxins, Digitalins und Digitaleins, Arch. f. exper. Path. u. Pharmakol. **3**: 274, 1875.
9. Ackermann: Quoted by Cushny, A. R.: The Action and Uses in Medicine of Digitalis and Its Allies, New York, 1925, Longmans, Green and Co.
10. Bock, H. E.: Zur Gefässwirkung des Strophanthins, Theozins und Coffeins; Untersuchungen an der überlebenden Extremität und an der überlebenden Lunge, Arch. f. exper. Path. u. Pharmakol. **166**: 634, 1932.
11. Jonescu, D., and Loewi, O.: Ueber eine spezifische Nierenwirkung der Digitaliskörper, Arch. f. exper. Path. u. Pharmakol. **59**: 71, 1908.
12. Joseph, D. R.: Untersuchungen über die Herz- und Gefässwirkungen kleiner Digitalisgaben bei intravenöser Injektion, Arch. f. exper. Path. u. Pharmakol. **73**: 81, 1913.

13. Eppinger, Hans, and Hess, L.: Versuche über die Einwirkung von Arzneimitteln auf überlebende Coronargefässe, Ztschr. f. exper. Path. u. Therap. **5**: 622, 1909.
14. Cow, Douglas: Some Reactions of Surviving Arteries, J. Physiol. **42**: 125, 1911.
15. Rabe, F.: Die Reaction der Kranzgefässe auf Arzneimittel (Nach Untersuchungen am überlebenden Warmblüterherzen), Ztschr. f. exper. Path. u. Therap. **11**: 175, 1912.
16. Voegtlin, Carl, and Macht, D. I.: The Action of Nitrites and Drugs of the Digitalis Group on the Isolated Coronary Artery, J. Pharmacol. & Exper. Therap. **5**: 77, 1913.
17. Bond, G. S.: Effect of Various Agents on the Blood Flow Through the Coronary Arteries and Veins, J. Exper. Med. **12**: 575, 1910.
18. Meyer, Felix: Ueber die Wirkung verschiedener Arzneimittel auf die Coronargefässe des lebenden Tieres, Arch. f. Anat. u. Physiol., p. 223, 1912.
19. Gunn, J. W. C.: The Influence of Temperature on the Action of Strophanthin on the Mammalian Heart, J. Pharmacol. & Exper. Therap. **6**: 39, 1914.
20. Sakai, S., and Saneyoshi, S.: Ueber die Wirkung einiger Herzmittel auf die Koronargefässe. (Strophantin, Coffein, Diuretin), Arch. f. exper. Path. u. Pharmakol. **78**: 331, 1915.
21. Bodo, Richard: The Effects of the "Heart-Tonics" and Other Drugs Upon the Heart-Tone and Coronary Circulation, J. Physiol. **64**: 365, 1928.
22. Fisher, Irvin, Guggenheimer, Hans, and Müller, E. A.: Ueber die Beeinflussung von Koronardurchblutung und Herztonus durch Theophyllinpräparate und Strophanthin nach Untersuchungen am Starlingschen Herz-Lungenpräparat, Deutsche med. Wchnschr. **2**: 1584, 1928.
23. Gilbert, N. C., and Fenn, G. K.: Effect of Digitalis on the Coronary Flow, Arch. Int. Med. **50**: 668, 1932.
24. Rühl, A., and Wiehler, A.: Ueber die Wirkung von Strophanthin auf den Gasstoffwechsel des insuffizienten Herzens, Arch. f. exper. Path. u. Pharmakol. **175**: 665, 1934.
25. Ginsberg, A. M., Stoland, O. O., and Siler, K. A.: Studies on Coronary Circulation. VI. The Effect of Some Members of the Digitalis Group on the Coronary Circulation, Am. Heart J. **16**: 663, 1938.
26. Rein, Hermann: Die Thermo-Stromuhr. Ein Verfahren zur fortlaufenden Messung der mittleren absoluten Durchflussmengen in uneröffneten Gefässen in situ, Ztschr. f. Biol. **87**: 394, 1928.
27. Hochrein, Max: Der Coronarkreislauf, Berlin, 1932, Julius Springer.
28. Essex, H. E., Herrick, J. F., Baldes, E. J., and Mann, F. C.: Digitalis and Coronary Blood Flow, Proc. Soc. Exper. Biol. & Med. **38**: 325, 1938.
29. Baldes, E. J., and Herrick, J. F.: A Thermostromuhr With Direct Current Heater, Proc. Soc. Exper. Biol. & Med. **37**: 432, 1937.
30. Essex, H. E., Herrick, J. F., and Visscher, M. B.: Influence of Certain Glucosides of Digitalis Lanata on the Coronary Blood Flow and the Blood Pressure in the Trained Dog, Am. Heart J. **16**: 143, 1938.
31. Hildebrandt, F., and Osterwald, Giessen: Strophanthin und Coronardurchblutung, Arch. f. exper. Path. u. Pharmakol. **190**: 209, 1938.
32. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. I. Effects on the Myocardial Cellular Structure, Am. Heart J. **25**: 648, 1943.
33. Herrick, J. F., and Baldes, E. J.: The Thermostromuhr Method of Measuring Blood Flow, Physics **1**: 407, 1931.
34. Hamilton, W. F., Brewer, George, and Brotman, Irving: Pressure Pulse Contours in the Intact Animal. I. Analytical Description of a New High-Frequency Hypodermic Manometer With Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, Am. J. Physiol. **107**: 427, 1934.

EXPERIMENTS WITH CALCULATED THERAPEUTIC AND TOXIC DOSES OF DIGITALIS

IV. Effects on the Cellular Structure of the Central Nervous System*

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THE purpose of the following studies was to ascertain whether therapeutic and toxic doses of digitalis are capable of producing demonstrable histologic changes in the brain and spinal cord of experimental animals. It is well known that digitalis in toxic amounts may produce transitory psychoses and other signs of cerebral disturbance among elderly patients. The question is raised whether some of these cerebral symptoms may not have their origin in structural as well as functional changes in the nerve cells of the brain.

LITERATURE

Withering,[1] who was the first physician to describe adequately the clinical use of digitalis, observed that the drug in toxic amounts affected the nervous system. He stated, "The foxglove when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death."

Since this publication, numerous writers have called attention to cerebral symptoms among patients who have received digitalis. Duroziez[2] reported twenty cases of "coma digitaliques." Hall[3, 4] described hallucinations and delirium in two patients who had received digitalis. Mackenzie[5] referred to headaches as the most frequent effect of digitalis on the central nervous system; he described several patients who exhibited "curious cerebral attacks." Hamburger,[6] in a study of five patients who had "acute cardiac psychoses," concluded that digitalis may contribute to a confusional state in patients whose circulation already is embarrassed severely. Carr[7] reported two cases of delirium caused by digitalis, and pointed out several important features on which the diagnosis depended. Plummer[8] warned against the over-

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digitalization of elderly patients. He attributed some of the deaths of patients suffering from cardiac disease to the toxic action of digitalis on the central nervous system. Christian,[9] Peabody,[10] and Conner[11] expressed similar opinions regarding the cerebral toxic effects of digitalis. Weiss[12] observed six instances of toxic psychoses among three hundred patients who received "up to toxic doses of digitalis." He attributed the psychosis to a sudden change of the cerebral circulation and to the physiochemical changes associated with the removal of large amounts of edema from the brain. Willius[13] called attention to the ominous nature of manifestations in the central nervous system after the administration of toxic doses of digitalis. Luten[14] stated that it was an open question whether the cerebral manifestations of digitalis intoxication were dependent on cerebral vascular effects or on direct action of digitalis on the brain.

We are not aware of any anatomic studies on the central nervous system of man or animals after the administration of toxic doses of digitalis.

METHODS

The same animals on which the anatomic studies on the myocardium[15] were made constituted the source of material for these histologic studies of the brain and spinal cord. Therefore, we need not review the details of the general experimental procedures.

It is necessary, however, to discuss the methods employed in studying the cellular structure of the central nervous system of these experimental animals. As we stated in a previous paper,[15] the cats were killed at various intervals after the administration of different doses of digitalis by placing the animals in an ether or chloroform chamber. The brain and spinal cord were removed as rapidly as possible. The entire brain was immersed in a 10 per cent solution of formalin for forty-eight hours; then small blocks of tissue were removed from the following regions: the left frontal cortex, the left motor cortex, the left visual cortex, the pons, and the cerebellum. These blocks of brain tissue were again immersed in a 10 per cent solution of formalin, and allowed to remain for forty-eight hours or more before they were sectioned and finally stained with cresyl violet. Small blocks of the cervical, thoracic, and lumbar portions of the spinal cord were treated similarly.

Care was taken not to use the brain of any animal on which necropsy was not performed immediately after the animal died or was killed. As a rule, only a few minutes elapsed from the time the animal died until the brain was in a 10 per cent solution of formalin.

The brains and spinal cords of twenty control cats were prepared and studied in a manner similar to that described for the experimental animals.

RESULTS

A. Histologic Studies on the Brain and Spinal Cord of the Control Animals.—The twenty control animals seemed to be in good health before they were killed. No macroscopic abnormalities were observed in the brain or spinal cord of any of them. Microscopic studies of the frontal, motor, and visual cortex revealed scattered, occasional, small pyramidal cells which appeared to be degenerating. There were, how-

ever, no zones of obvious necrosis and extensive degeneration such as were seen in some of the animals which received digitalis. No degenerative changes were observed in the larger pyramidal cells of the cerebral cortex. No evidence of cellular degeneration was seen in the cerebellum, pons, or spinal cord. The blood vessels of the central nervous system seemed to be free from histologic evidence of arteriosclerosis.

B. Histologic Studies on the Brain and Spinal Cord of Animals Which Had Received Calculated Therapeutic Doses of Digitalis.—Two types of experiments were designed to ascertain the effects of calculated therapeutic doses of digitalis on the cellular structure of the central nervous system. To one group of animals (Group A), the calculated therapeutic amount of the drug was administered in a single dose within a period of two to three minutes, or it was given in divided doses over a period of twenty-four to forty-eight hours. The brain and spinal cord were examined microscopically from six to fifty-six days after the drug had been administered. To the other group of animals (Group B), the calculated therapeutic dose of digitalis was administered as in Group A, but, in addition, an estimated daily maintenance dose of the drug was given to the animals over a period of nineteen to sixty days. The daily maintenance dose for the cat was estimated on the basis of body weight to correspond to 1 or 2 cat units for a man weighing 70 kg.[15] The brain and spinal cord of the animals in Group B also were examined histologically nineteen to sixty days after the administration of the digitalis had been started.

TABLE I

CALCULATED THERAPEUTIC DOSES OF DIGITALIS AND DURATION OF THE EXPERIMENT

GROUP A

DRUG USED	DOSE, PER CENT OF MINIMAL LETHAL DOSE	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS
Lanatoside A	20	Single dose, intravenous	14
Digalen	30	Single dose, intravenous	6
Lanatoside C	30	Single dose, intravenous	11
Digitoxin	30	Single dose, intravenous	11
Lanatoside A	30	Single dose, intravenous	12
Lanatoside A	30	Divided doses (48 hr.), intramuscular	12
Lanatoside A	30	Divided doses (48 hr.), intravenous	12
Digalen	30	Single dose, intravenous	14
Digitoxin	30	Single dose, intravenous	14
Lanatoside A	30	Single dose, intravenous	18
Lanatoside A	30	Single dose, intravenous	21
Digifortis	30	Single dose, oral	56

In Group A there were twelve cats (Table I). No anatomic changes were found in the brain and spinal cord of any of the animals which had received calculated therapeutic amounts of digitalis, either in single or divided doses.

In Group B there were eleven cats (Table II). The object of the experiments in this group was to ascertain whether demonstrable mor-

TABLE II

DAILY ADMINISTRATION OF THE EQUIVALENT OF 1 OR 2 CAT UNITS OF DIGITALIS TO CATS DIGITALIZED PREVIOUSLY WITH 30 PER CENT OF MINIMAL LETHAL DOSE

GROUP B

DRUG USED	EQUIVALENT DAILY DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS
Digalen	1	Intravenous	19
Digifortis	1	Oral	19
Digifortis	1	Oral	30
Digalen	1	Intravenous	34
Lanatoside A	1	Intravenous	36
Digiglusin	2	Intravenous	20
Digifortis	2	Oral	30
Digalen	2	Intravenous	30
Lanatoside A	2	Intravenous	36
Digalen	2	Intravenous	40
Digifortis	2	Oral	60

phologic changes would develop in the central nervous system of digitalized animals which received daily maintenance doses of the drug within the range of doses used in man. Five of the animals which were digitalized with calculated therapeutic doses of digitalis (30 per cent of the minimal lethal dose) received daily maintenance doses that were estimated to be approximately equivalent, on the basis of the body weight of the cat, to 1 cat unit daily for a man weighing 70 kg. The remaining six animals were also digitalized with 30 per cent of the minimal lethal dose of the drug, and then given daily the estimated equivalent of 2 cat units. The body weight of the cat and that of a 70-kilogram man were again used as the basis for the calculations.

No definite cellular changes developed in the brain or spinal cord of any of the animals in Group B, even when the drug was administered daily for two months.

Drowsiness or other recognizable signs of disturbance of the central nervous system were not observed in any of the cats in Group A or B.

C. Histologic Studies on the Brain and Spinal Cord of Animals Which Had Received Toxic Doses of Digitalis. (a) Observations correlating dosage, duration of experiment, and histologic studies—As has been stated elsewhere,[15] grouping the animals in this series was difficult, for the number of animals was rather large, and the manner in which the different digitalis bodies were administered varied considerably. In order to simplify the presentation, the animals were arranged in two major groups: (1) Group A_1, those animals which received single toxic doses of digitalis and subsequently had the brain and spinal cord examined microscopically after various periods; (2) Group B_1, those animals which received multiple doses of digitalis in various toxic amounts over different periods and then had their central nervous systems subjected to histologic study.

Table III shows the amounts of the various single doses of digitalis bodies, the route of administration, the duration of the experiment after

Table III

Correlation of Single Toxic Dose of Digitalis, Duration of the Experiment, and Histologic Study of the Central Nervous System

Group A_1

Drug Used	Dose, Per Cent of Minimal Lethal Dose	Method of Administration	Duration of Experiment	Histologic Changes			
				Cerebrum	Cerebellum	Pons	Spinal Cord
Digalen	40	Intravenous	12 days	No	No	No	No
Digiglusin	40	Intravenous	12 days	No	No	No	No
Lanatoside A	40	Intravenous	12 days	–	–	–	–
Lanatoside C	50	Intravenous	11 days	No	No	No	No
Digitoxin	50	Intravenous	13 days	No	No	No	No
Lanatoside A	50	Intravenous	14 days	No	No	No	No
Digalen	50	Intravenous	15 days	No	No	No	No
Digitoxin	60	Intravenous	12 hours	–	–	–	–
Lanatoside C	60	Intravenous	9 days	No	No	No	No
Lanatoside A	60	Intravenous	10 days	No	No	No	No
Digitoxin	60	Intravenous	10 days	Yes	Yes	No	–
Lanatoside C	60	Intravenous	11 days	Yes	Yes	No	No
Digiglusin	60	Intravenous	12 days	No	No	No	No
Digalen	60	Intravenous	14 days	No	No	No	No
Digalen	60	Intravenous	15 days	No	No	No	No
Lanatoside A	60	Intravenous	15 days	No	No	No	No
Digitoxin	70	Intravenous	4 days	No	No	No	No
Lanatoside C	70	Intravenous	11 days	No	No	No	No
Digiglusin	70	Intravenous	12 days	Yes	Yes	No	No
Digiglusin	75	Intravenous	3 days	No	No	No	No
Digiglusin	75	Intravenous	9 days	–	–	–	–
Lanatoside A	75	Intravenous	12 days	Yes	Yes	Yes	Yes
Digiglusin	80	Intravenous	39 min.	–	–	–	–
Lanatoside A	80	Intravenous	3 hours	–	–	–	–
Lanatoside A	80	Intravenous	4 hours	–	–	–	–
Lanatoside A	80	Intravenous	6½ hours	–	–	–	–
Digalen	80	Intravenous	1 day	No	No	No	No
Lanatoside A	80	Intravenous	2 days	–	–	–	–
Lanatoside A	80	Intravenous	3 days	No	No	No	No
Digalen	80	Intravenous	4 days	No	No	No	No
Lanatoside A	80	Intravenous	5 days	No	No	No	No
Digitoxin	80	Intravenous	6 days	Yes	Yes	Yes	Yes
Lanatoside A	80	Intravenous	7 days	No	No	No	No
Lanatoside A	80	Intravenous	8 days	Yes	Yes	Yes	Yes
Lanatoside C	80	Intravenous	9 days	No	No	No	No
Lanatoside A	80	Intravenous	10 days	No	No	No	No
Lanatoside A	80	Intravenous	10 days	No	No	No	No
Lanatoside C	80	Intravenous	11 days	No	No	No	No
Lanatoside A	80	Intravenous	12 days	Yes +++	Yes ++	Yes +	± ?
Digalen	80	Intravenous	12 days	–	–	–	–
Digiglusin	80	Intravenous	12 days	?	No	No	No
Lanatoside B	80	Intravenous	12 days	Yes ++++	Yes ++	Yes ++	Yes +
Digitoxin	80	Intravenous	12 days	–	–	–	–
Tincture digitalis	80	Intravenous	12 days	No	No	No	No
Digifortis	80	Oral	13 days	?	No	No	No
Lanatoside A	80	Intravenous	14 days	No	No	No	–
Digalen	80	Intravenous	14 days	No	No	No	No
Lanatoside A	80	Intravenous	16 days	Yes	Yes	Yes	No
Digalen	80	Intravenous	17 days	Yes	Yes	–	–
Lanatoside A	80	Intravenous	21 days	No	No	No	No
Lanatoside A	80	Intravenous	23 days	Yes	Yes	Yes	Yes
Digalen	80	Intravenous	24 days	Yes	Yes	Yes	Yes
Digalen	80	Intravenous	30 days	No?	No	No	No
Lanatoside A	80	Intravenous	30 days	No?	–	–	–
Digalen	80	Intravenous	42 days	No?	No	No	–
Digalen	80	Intravenous	60 days	No	No	No	No

the drug was administered, and the results of the histologic examination of several parts of the central nervous system. The data summarized in this table indicate the following:

1. No significant anatomic changes were observed in the brain and spinal cord after the administration of either 40 or 50 per cent of the minimal lethal dose.

2. Cellular changes were observed in the cerebral cortex and in the cerebellum in two of eight cats which had received 60 per cent of the minimal lethal dose.

3. When the dose was raised to 70, 75, or 80 per cent of the minimal lethal dose, the frequency of cellular changes increased.

4. Regardless of the size of any single dose of the drug, no definite cerebral lesions were seen during the first five days.

5. When histologic changes occurred after the administration of single doses of digitalis, they were almost always present between the sixth and the twelfth day.

6. The cellular changes in the central nervous system were produced by digitalis whole leaf or crystalline products of digitalis (digitoxin, lanatoside A, B, and C).

7. Lesions did not develop in the brains of all the animals which received toxic doses of digitalis, even when the duration of the experiment was six days or more (that is, within the period during which lesions are producible).

Although it is interesting to know the minimal amount of digitalis which will produce degenerative changes in the central nervous system when the drug is given in a single dose, it is more important from the standpoint of clinical application to ascertain the minimal amount which will cause damage of the nerve cells when the drug is administered daily over a given period, as in treating patients. With this idea in mind, a series of animals was digitalized with 30 per cent of the minimal lethal dose and then subjected to estimated daily doses of digitalis within the toxic range. These daily doses were estimated in the manner described in a previous paper;[15] instead of administering the daily equivalent of 1 or 2 cat units, the animals were given daily amounts corresponding to 3, 4, 5.5, or 6 cat units (let it be recalled again that the body weight of the cat and that of a 70-kilogram man were used as the basis for these calculations).

Table IV summarizes the relation between these various daily toxic doses of digitalis, administered over different periods, and the histologic studies of the brain and spinal cord. The following observations are indicated in Table IV:

1. Definite evidence of cellular degeneration was observed in the central nervous system of seven of eleven animals. In one animal the changes were not very prominent. In three cats no distinct cerebral, cerebellar, pontine, or spinal cord lesions were observed.

2. Three animals were found dead. Their central nervous systems

TABLE IV

CORRELATION OF THE HISTOLOGIC STUDIES OF THE CENTRAL NERVOUS SYSTEM, THE DURATION OF THE EXPERIMENT, AND THE DAILY ADMINISTRATION OF THE EQUIVALENT OF 3, 4, 5.5, OR 6 CAT UNITS OF DIGITALIS TO CATS DIGITALIZED WITH 30 PER CENT OF THE MINIMAL LETHAL DOSE

GROUP B_1

DRUG USED	DAILY EQUIVALENT DOSE, CAT UNITS	METHOD OF ADMINISTRATION	DURATION OF EXPERIMENT, DAYS	HISTOLOGIC CHANGES			
				CEREBRUM	CEREBELLUM	PONS	SPINAL CORD
Digitoxin	3	Intravenous	5	Yes	Yes	Yes	Yes
Digifortis	3	Oral	11	–	–	–	–
Tincture digitalis	3	Intravenous	13	–	–	–	–
Tincture digitalis	3	Intravenous	14	No	No	No	No
Tincture digitalis	3	Intravenous	18	No	No	No	No
Lanatoside A	3	Intravenous	25	Yes	Yes	?	?
Lanatoside A	3	Intravenous	25	Yes	Yes	Yes	Yes
Lanatoside C	3	Intravenous	30	No	No	No	–
Digiglusin	4	Intravenous	7	Yes	Yes	No	No
Digifortis	4	Oral	14	–	–	–	–
Digifortis	4	Oral	19	Yes	Yes	Yes	Yes
Digifortis	4	Oral	30	Yes	Yes	Yes	–
Lanatoside A	5.5	Intravenous	30	Yes	Yes	Yes	Yes
Digifortis	6	Oral	30	Yes	Yes	Yes	–

were not removed for microscopic examination, for we did not wish to have our studies confused by uncontrolled post-mortem changes.

(b) Cellular changes observed in the central nervous system after the injection of toxic doses of digitalis.—It should be recalled that calculated therapeutic doses of digitalis did not produce any significant anatomic changes in the central nervous system.

Toxic doses of digitalis, as indicated in Tables III and IV, did produce degenerative changes in the central nervous system. The extensiveness and intensity of the cellular changes varied with the amount of digitalis, the manner in which it was administered, and the age of the animal. As a rule, the higher the dose of digitalis, the greater was the histologic change in the central nervous system. This observation, however, was modified chiefly by two factors: (1) the lesions were more extensive after the administration of repeated doses of digitalis in the toxic range than after the administration of single toxic doses; (2) the older the animal, the more likely one was to observe cellular changes in the brain.

The frequency and intensity of the cellular changes varied in different parts of the central nervous system. Lesions were most likely to be found in the cerebral cortex, and least likely to be observed in the spinal cord. Although the degenerative changes were extensive in the cerebral cortex at times, they were never very prominent in the spinal cord. The Purkinje cells in the cerebellum showed evidence of degen-

eration when cortical lesions were prominent. The frequency of cellular degeneration in the pons was greater than in the spinal cord, but it was definitely less than in the cerebral cortex.

The cortical degenerative changes tended to occur in small groups of cells. Groups of degenerating pyramidal cells (large and small) were frequently surrounded by anatomically normal cells. This may have some significance when one considers the manner in which the arterial branches from the meninges supply limited zones of cortical tissue. Campbell[16] has adequately described this distribution of the cortical blood supply in the cat. At times the cortical lesions were extensive, and the degeneration involved the majority of the cells. Animals which showed these extensive and advanced lesions of the central nervous system were obviously ill (drowsy, anoretic, spastic, and so forth).

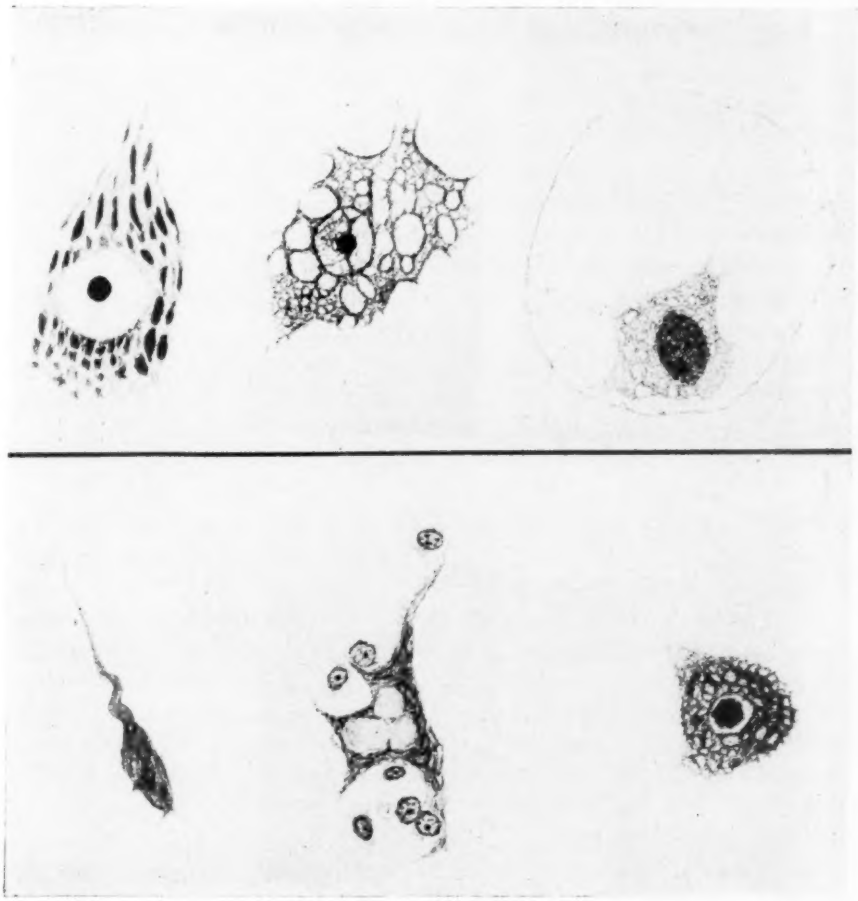

Fig. 1.—Drawing of nerve cells from the cat. Top row, left: normal pyramidal cell from cortex; top row, center: vacuolization in cortical pyramidal cell; top row, right: advanced degeneration in cortical pyramidal cell; bottom row, left: pyknosis in cortical pyramidal cell; bottom row, center: satellitosis in cortical pyramidal cell; bottom row, right: degeneration in cerebellar Purkinje cell.

The following types of significant and definite changes were noted in the cerebral cortex after toxic doses of digitalis had been given:

1. Swollen cells. The pyramidal cells became enlarged; the normal concave contours between the individual processes were replaced by less concave contours or by convex outlines; the cytoplasm usually accepted the stain poorly.

2. Vacuolization. The cytoplasm became rather obviously filled with vacuoles (Fig. 1). These replaced the tigroid Nissl substance of the normal pyramidal cell (Figs. 1 and 2).

3. Degeneration. The cytoplasm underwent vacuolization, degeneration, and, finally, liquefaction. When the cytoplasm of the cell had been completely liquefied, one saw only a ghost area in the cortex in which the cell had once been located. Fig. 1 illustrates one of the stages in this process of degeneration.

4. Pyknosis. The cytoplasm shrank and stained more or less uniformly and deeply with cresyl violet (Fig. 1).

5. Satellitosis. The degenerating pyramidal cell was surrounded by small oligodendroglial cells (Fig. 1).

There was nothing specific about the character of these cellular changes. They have been described by many authors in various anoxic conditions (see literature in the sixth paper of this series).[17]

Degenerative changes were seen also in the Purkinje cells of the cerebellum. Fig. 1 shows a Purkinje cell which was undergoing degenerative change.

Similar degenerative changes occurred in the neurons of the pons and the spinal cord, but the lesions were not striking or extensive. Of the portions of the central nervous system which were examined, the cerebral cortex (Fig. 3) was the most vulnerable to toxic doses of digitalis.

If the animal did not die from the toxic dose or doses of digitalis, it recovered completely. It was difficult to recognize anatomic changes in the brains of the animals thirty to sixty days after they had received a toxic dose of digitalis and had recovered.

(c) The factor of age in the production of cerebral lesions.—As in the case of the myocardial lesions,[15] the older animals were more prone than the younger ones to manifest degenerative changes in the pyramidal cells of the cerebral cortex after they had been given toxic doses of digitalis. This difference in the reaction to digitalis could not be accounted for by arteriosclerosis in the older animals, for no evidence of this disease was found in either the arteries or the arterioles of any of the experimental animals.

(d) Observations on signs of intoxication of the central nervous system in cats treated with digitalis.—Drowsiness and, at times, ataxia, with spastic reflexes, were noted in some of the animals from the fifth to the fourteenth day. Several animals died of respiratory failure, which had been preceded by Cheyne-Stokes respiration. If the digitalis

did not cause death by respiratory failure or cardiac failure, the animals recovered, and, to all intents and purposes, were normal.

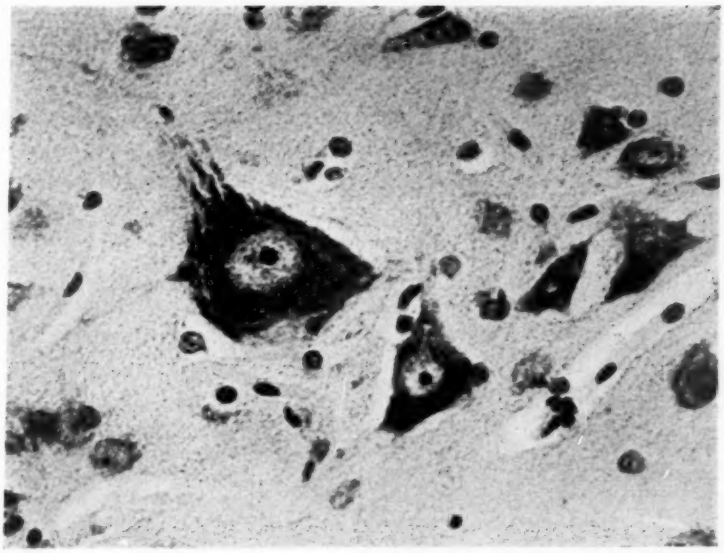

Fig. 2.—Normal pyramidal cell in the motor cortex of control cat. Note the distribution of the Nissl substance (×450).

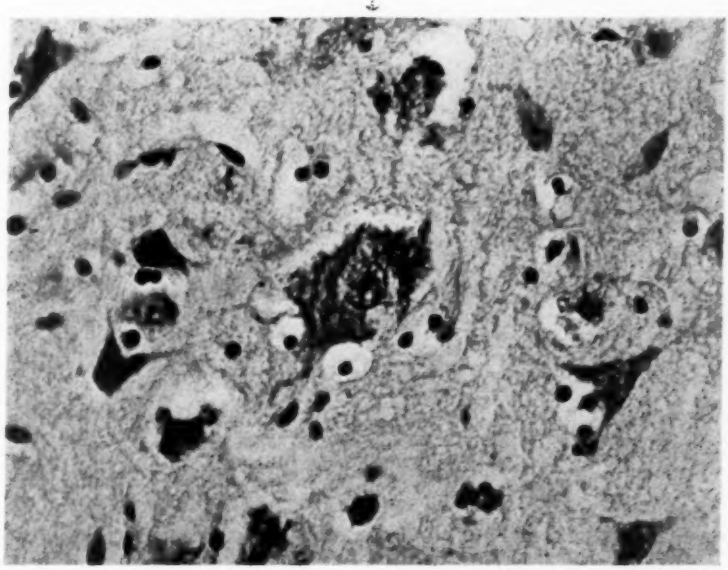

Fig. 3.—Advanced degeneration of the pyramidal cells of the motor cortex twelve days after the injection of a toxic dose of digitalis (75 per cent of the minimal lethal dose of lanatoside A). The animal was drowsy and exhibited spastic reflexes before it was killed (×450).

SUMMARY

No significant cellular changes were observed in the brain and spinal cord after the administration of calculated therapeutic amounts of digitalis (30 per cent of the minimal lethal dose) in single or in divided doses. The histologic studies were made after a minimum of six days and a maximum of fifty-six days.

No cellular changes were produced in our experimental animals when they were digitalized rapidly with a calculated therapeutic dose of digitalis and then were given maintenance doses of the drug which were estimated to correspond to either 1 or 2 cat units for a man weighing 70 kg. The histologic studies were made after a minimum of nineteen days and a maximum of sixty days.

In our experiments, 60 per cent of the minimal lethal dose was the smallest amount which, when given as a single dose, produced definite evidence of cellular degeneration in the cerebral cortex. This dose of digitalis was in the toxic range.

The frequency with which lesions of the central nervous system occurred increased as the size of the single dose of digitalis was increased to 80 per cent of the minimal lethal dose.

Cerebral lesions were not observed until six or more days after single toxic doses of digitalis had been administered.

Histologic changes were not observed in the central nervous systems of all of the animals which had received toxic amounts of digitalis, even when the quantity of the drug was 80 per cent of the minimal lethal dose.

Degenerative changes were produced in the central nervous system when the animals were digitalized rapidly with a calculated therapeutic dose of digitalis and then were given daily quantities of the drug which were estimated to correspond to 3, 4, 5.5 or 6 cat units for a man weighing 70 kg. The equivalent of 3 cat units daily of parenterally administered digitoxin caused lesions in the brain and spinal cord within five days in one animal, and a corresponding daily dose of orally administered tincture of digitalis produced cellular changes in the central nervous system within eleven days in one animal. The central nervous systems of the digitalized animals in the group which had received daily doses of digitalis in the toxic range were examined microscopically after a minimum of five days and a maximum of thirty days.

The cellular changes in the brain after the administration of digitalis were not specific. The following cellular alterations were observed in the large and small pyramidal cells of the cerebral cortex: swelling of the cell body; vacuolization of the cytoplasm; varying grades of cytoplasmic and nuclear degeneration, up to complete liquefaction of the cell; pyknosis of the cells; and cellular degeneration plus satellitosis.

The cerebral changes often occurred in localized zones, with normal cortical cells in the surrounding tissue. The lesions were at times diffuse when large doses of digitalis had been administered.

Old animals were more prone than young ones to manifest cerebral lesions after the administration of digitalis. This difference of sensitivity to the drug was not related to arteriosclerosis; at least no evidence of this disease was observed in any of the arteries or the arterioles of the central nervous system.

Drowsiness and spastic reflexes were observed in the animals which were markedly intoxicated with digitalis.

Animals which survived the administration of the toxic doses of digitalis recovered completely in three to four weeks.

REFERENCES

1. Withering, William: An Account of the Foxglove, and Some of Its Medical Uses; With Practical Remarks on Dropsy, and Other Diseases, M. Classics **2**: 295, 1937.
2. Duroziez, P.: Quoted by Hall, H. O.[4]
3. Hall, H. O.: The Hallucinations of Digitalis. Does Digitalis Cause Hallucinations, Delirium or Insanity Under Certain Conditions? Am. Med. **1**: 598, 1901.
4. Hall, H. O.: The Delirium and Hallucinations of Digitalis, Am. Med. **9**: 489, 1905.
5. Mackenzie, James: Digitalis, Heart **2**: 273, 1911.
6. Hamburger, W. W.: Acute Cardiac Psychoses: Analysis of the Toxic and Circulatory Factors in 5 Cases of Acute Confusion, M. Clin. North America **7**: 465, 1923.
7. Carr, J. G.: Digitalis Delirium, M. Clin. North America **9**: 1391, 1926.
8. Plummer, H. S.: Use of Digitalis in Hyperthyroid Cases, J. A. M. A. **84**: 1868, 1925.
9. Christian, H. A.: Discussion, J. A. M. A. **84**: 1868, 1925.
10. Peabody, F. W.: Discussion, J. A. M. A. **84**: 1868, 1925.
11. Conner, L. A.: Discussion, J. A. M. A. **84**: 1868, 1925.
12. Weiss, Soma: The Effects of the Digitalis Bodies on the Nervous System: an Analysis of the Mechanism of Cardiac Slowing, Nausea and Vomiting, Psychosis, and Visual Disturbance Following Digitalis Therapy, M. Clin. North America **15**: 963, 1932.
13. Willius, F. A.: Cardiac Clinics. XIV. Digitalis Poisoning With Cerebral Symptoms; Coronary Sclerosis With Angina Pectoris, and Paroxysmal Dyspnea, Proc. Staff Meet., Mayo Clin. **10**: 649, 1935.
14. Luten, Drew: The Clinical Use of Digitalis, Springfield, Ill., 1936, Charles C Thomas.
15. Dearing, W. H., Barnes, A. R., and Essex, H. E.: Experiments With Calculated Therapeutic and Toxic Doses of Digitalis. I. Effects on the Myocardial Cellular Structure, AM. HEART J. **25**: 648, 1943.
16. Campbell, A. C. P.: The Vascular Architecture of the Cat's Brain; a Study by Vital Injection, A. Research Nerv. & Ment. Dis., Proc. **18**: 69, 1938. The Circulation of the Brain and Spinal Cord; a Symposium on Blood Supply, Baltimore, 1938, Williams & Wilkins Co., vol. 18, pp. 69-93.
17. Dearing, W. H., Barnes, A. R., Boothby, W. M., and Essex, H. E.: Unpublished data.

THE EFFECTS OF DIGITALIS, URGININ, CONGESTIVE CARDIAC FAILURE, AND ATROPINE ON THE HYPERACTIVE CAROTID SINUS

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ALTHOUGH studies on the carotid sinus reflex[1-5] in animals and man have established that the activity of the reflex is increased by congestive cardiac failure or by digitalis, little is known of the relative influence of these two factors.

Weiss, Baker, Capps, and Ferris[6, 7] and Nathanson[8] have demonstrated that syncopal states produced by pressure over the carotid sinus simulate the spontaneous syncope which affects patients with a hyperactive carotid sinus reflex. In these and other studies it has been shown that the cardiac responses to carotid sinus stimulation can be controlled either by epinephrine (and related compounds) or by atropine. Since coronary disease and arterial hypertension are likely to be associated with hyperactivity of the carotid sinus reflex,[9, 10] epinephrine may be contraindicated,[11, 12, 13] whereas moderate doses of atropine are well tolerated by such patients. However, the effect of atropine on a reflex arc which includes the vagus as an efferent pathway is complex. In 1880, Anrep,[14] and, in 1891, Mueller[15] demonstrated that the initial action of atropine was to slow the pulse rate and the late effect was to accelerate it. Petzetakis,[16] in a study of the oculocardiac reflex, demonstrated that the early effect of atropine was to accentuate the slowing of the heart produced by pressure over the eyes. The late effect of atropine tended to abolish the reflex slowing of the heart. He concluded that the early effect of atropine was "due to an increase in the excitability of the cardiomoderator elements contained in the vagi." The late effect of atropine on the oculocardiac reflex was the result of paresis of the vagal endings. These observations have been corroborated and elaborated by numerous investigations.[17-21] In all reports of the effect of atropine on stimulation of the carotid sinus, only the paralyzing properties of atropine have been considered.

We have studied certain modifications produced by therapeutic doses of atropine on the results of stimulation of the hyperactive carotid sinus reflex. In addition, we have observed the relative effects of digitalis, urginin, and congestive cardiac failure on stimulation of the carotid sinus. Urginin was used to ascertain whether another cardiotonic drug would have effects similar to those of digitalis.

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MATERIAL

A group of eight patients who complained of recurring syncope or severe faintness were selected. Previous observations had shown that the cerebral symptoms of these patients were reproduced by pressure at the bifurcation of one or both of the carotid arteries. An associated ventricular pause was usually produced. In one patient such effects were abolished by local anesthesia and subsequent denervation of the sinuses.

Most of the patients had congestive cardiac failure, with or without angina pectoris.

PROCEDURE

At suitable intervals the above patients were seated in a comfortable chair and the heart rate was obtained by an electrocardiographic tracing. The carotid sinus was then stimulated by applying pressure at the bifurcations of the carotid arteries, and the activity of the sinus reflex was ascertained by the slowing of the ventricular rate produced by such pressure. When stimulation of the sinus resulted in slowing of the ventricles, "R-R-intervals" were measured. Such intervals represent the average duration of the ventricular complexes which occurred during a constant period of stimulation. If stimulation of the carotid sinus made an R-R interval longer than 3.6 seconds, the actual duration of the pause was recorded, and no average value was taken.

To avoid variations in stimulation, firm pressure was made with three fingers over the bifurcations of the carotid arteries, and the sinuses were vigorously massaged. Pressure was usually maintained for more than fourteen seconds. Occasionally this interval had to be shortened because the patient's necks became tender from the vigorous massaging. Repeated stimulations were separated by ten-minute rest periods, for bizarre results occasionally occurred when pressure was made at shorter intervals. The pressure points were intentionally shifted, and the maximum effect obtained from three periods of stimulation was used for comparative purposes. In the prolonged atropine experiments the pressure points were constant after the initial control periods.

The carotid sinuses of two patients were in close approximation to the larynx, and pressure occasionally caused marked coughing; in one case the carotid artery was so large and tortuous that it was sometimes difficult to maintain sustained massage of the artery. The results obtained from such unsatisfactory stimulation were discarded. In two cases the less sensitive side was selected for study, but a fairly marked response was generally obtained except in the case of A. G., who previously had had a bilateral stripping operation upon the carotid arteries.

Digitalis was used in 0.1 Gm. pills, made from a standard powdered leaf. Urginin was used in 0.5 mg. oral tablets. The effects of urginin on congestive cardiac failure and the electrocardiogram have been adequately reviewed.[22, 23] Equivalent therapeutic doses of these drugs were taken in small quantities until changes in the electrocardiograms were observed or minor toxic manifestations had occurred. The electrocardiographic indications of digitalis activity in our cases were greatly restricted, for slowing of the heart and changes in conduction intervals might occur because of the hyperactive carotid sinus reflex. Changes in the electrocardiograms are indicated in Table I by the sign "?" when they did not seem to be chiefly caused by the cardiotonic drugs. The drugs were continued in maintenance amounts until their influence on the carotid sinus could be ascertained. Occasionally, larger quantities of the drugs were used initially, but, in such rare instances, small doses were taken for a minimum of forty-eight hours preceding sinus massage. The infrequent departures from the standard method of administration were necessary to relieve myocardial failure. One glucoside was usually discontinued for at least three weeks before the second was started.

TABLE I

DAILY MAINTENANCE DOSE OF THE CARDIOTONIC DRUGS AND RESULTING ELECTROCARDIOGRAPHIC CHANGES

DATE	DAILY R	EKG CHANGES
	Case 1 (R. McA.)	
11/ 2/38	Urg. 1.5 mg.	Moderate S-T I, II, III
2/23/39	Urg. 1.5 mg.	Slight S-T I, II, III
4/ 6/39	Dig. 0.1 Gm.	Marked S-T I, II, III
1/30/40	Dig. 0.3 Gm.	Marked S-T I, II, III
2/ 3/40	Dig. 0.3 Gm.	Marked S-T I, II, III
2/17/40	Dig. 0.2 Gm.	Marked S-T I, II, III
	Case 2. (F. S.)	
8/26/38	Dig. 0.15 Gm.	Moderate S-T I, II, III
10/ 8/38	Urg. 1.5 mg.	Moderate S-T I, II
12/10/38	Urg. 1.5 mg.	Moderate S-T I, II, III
5/ 1/39	Dig. 0.2 Gm.	Moderate S-T I, II, III
6/19/39	Dig. 0.2 Gm.	Moderate S-T I, II
7/10/39	Dig. 0.2 Gm.	Moderate S-T II*
9/ 9/39	Dig. 0.2 Gm.	Moderate S-T I, II
4/11/40	Urg. 1.5 mg.	Moderate S-T I, II
4/27/40	Urg. 1.0 mg.	Moderate S-T I, II
6/10/40	Dig. 0.15 Gm.	Moderate S-T I, II
9/11/40	Dig. 0.15 Gm.	Moderate S-T I, II
11/30/40	Dig. 0.15 Gm.	Moderate S-T I, II
3/26/41	Urg. 2.0 mg.	Moderate S-T I, II
7/12/41	Dig. 0.15 Gm.	Moderate S-T I, II
	Case 3. (A. G.)	
11/28/38	Urg. 2.0 mg.	Moderate S-T I, II, III
12/12/38	Urg. 1.0 mg.	Moderate S-T I, II, III
1/11/39	Urg. 1.0 mg.	Slight S-T I, II
2/ 9/39	Dig. 0.2 Gm.	Slight S-T I, II, III
5/ 8/39	Dig.†	None
7/29/41	Dig. 0.3 Gm.	Marked S-T I, II
	Case 4. (H. Z.)	
2/24/39	Dig. 0.2 Gm.	?
5/ 1/39	Dig. 0.3 Gm.	?
6/16/39	Dig. 0.2 Gm.	?
7/17/39	Dig. 0.2 Gm.	?
4/30/41	Urg. 2.0 mg.	?
5/19/41	Urg. 2.0 mg.	?
	Case 5. (I. R.)	
12/ 2/38	Urg. 1.5 mg.	?
12/19/38	Urg. 1.5 mg.	?
1/ 5/39	Urg. 1.0 mg.	?
2/ 7/39	Dig. 0.1 Gm.	?

Dig.: Digitalis Folia. Urg.: Urginin. ? EKG: when electrocardiographic abnormalities were not definitely attributable to the drugs, there were often abnormalities of T and S-T.

*Leads I, III not taken.

†C. S. P. 1 hr. 12 min. after 14 c.c. digalen I.V.

Standard tablets of atropine were dissolved in 1 c.c. of sterile water and injected subcutaneously in the right deltoid region. Doses of 0.0012 Gm. (gr. 1/50) and 0.0018 Gm. (gr. 1/33) were used. These quantities sometimes caused dryness of the mouth and a disturbance in vision which occurred, for the most part, after the periods of observation. The reactions were not so severe as to preclude future cooperation on the part of the patients. Partial paralysis of the vagus was produced slowly enough to allow sufficient time to study the varying effects of atropine.

TABLE II

RESULTS OF ATROPINE OBSERVATIONS IN 5 CASES

CASE	DATE	R	TIME	R-R INT. REST	R-R INT. C.S.P.	DATE	R	TIME	R-R INT. REST	R-R INT. C.S.P.	DATE	R	TIME	R-R INT. REST	R-R INT. C.S.P.
1	2/22/39	Urg. 1.5 mg.	Control	0.72	1.14	2/ 6/39	None	Control	0.66	1.06	4/ 6/39	Dig. 0.1 Gm.	Control	0.74	1.43
			—Atr.	0.0012	Gm.—			—Atr.	0.0012	Gm.—			—Atr.	0.0012	Gm.—
			5 min.	0.85	1.10			5 min.	0.68	1.14			5 min.	0.79	1.51
			9 min.	0.69	0.89			15 min.	0.57	1 19			14 min.	0.74	1.04
			19 min.	0.53	0.95			28 min.	0.52	0.81			24 min.	0.68	0.93
			29 min.	0.52	0.83			36 min.	0.53	0.70			34 min.	0.64	1.03
			44 min.	0.58	1.18			48 min.	0.53	0.75			45 min.	0.65	0.95
			54 min.	0.62	0.85			55 min.	0.56	0.88			54 min.	0.63	0.91
			64 min.	0.61	1.04										
2	12/10/38	Urg. 1.0 mg.	Control	1.05	8.12	2/17/39	None	Control	1.00	1.14	3/28/39	None	Control	0.96	11.50
			—Atr.	0.0012	Gm.—			—Atr.	0.0012	Gm.—			—Atr.	0.0012	Gm.—
			10 min.	1.12	11.48			5 min.	1.02	1.61			8 min.	0.98	11.90
			20 min.	0.86	5.70			15 min.	0.96	1.13			20 min.	0.90	6.60
			40 min.	0.84	1.81			37 min.	0.74	0.90			31 min.	0.92	1.60
			55 min.	0.97	2.07			50 min.	0.72	0.91			41 min.	0.77	1.17
			70 min.	0.95	4.48			60 min.	0.75	0.83			51 min.	0.78	1.29
3	12/12/38	Urg. 1.0 mg.	Control	1.40	1.47	1/11/39	Urg. 1.0 mg.	Control	1.26	1.60	2/ 9/39	Dig. 0.1 Gm.	Control	1.26	1.63
			—Atr.	0.0012	Gm.—			—Atr.	0.0018	Gm.—			—Atr.	0.0018	Gm.—
			5 min.	1.45	1.70			5 min.	1.30	1.66			5 min.	1.27	1.54
			10 min.	1.41	1.50			11 min.	1.29	1.65			10 min.	1.27	1.46
			25 min.	1.33	1.41			21 min.	1.21	1.37			26 min.	1.20	1.27
			31 min.	1.30	1.37			31 min.	1.05	1.18			37 min.	1.18	1.32
			41 min.	1.28	1.38			41 min.	1.07	1.13			47 min.	1.21	1.30
			48 min.	1.34	1.43			47 min.	1.16	1.21			57 min.	1.22	1.29
			58 min.	1.34	1.40										
4	1/ 3/39	Urg. 1.5 mg.	Control	0.70	6.30	1/19/39	None	Control	0.70	4.66	2/24/39	Dig. 0.2 Gm.	Control	0.80	3.80
			—Atr.	0.0012	Gm.—			—Atr.	0.0018	Gm.—			—Atr.	0.0018	Gm.—
			5 min.	0.81	4.00			6 min.	0.75	6.70			5 min.	0.83	4.82
			11 min.	0.87	5.40			13 min.	0.77	1.07			10 min.	0.88	1.51
			21 min.	0.84	3.82			23 min.	0.56	0.75			25 min.	0.74	0.99
			31 min.	0.69	0.83			33 min.	0.52	0 61			35 min.	0.60	0.83
			41 min.	0.66	1.07			43 min.	0.53	0.66			47 min.	0.58	0.74
			51 min.	0.66	0.96			54 min.	0.54	0.70					
5	1/ 5/39	Urg. 1.0 mg.	Control	0.88	4.42						2/ 7/39	Dig. 0.1 Gm.	Control	0.87	7.46
			—Atr.	0.0012	Gm.—								—Atr.	0.0012	Gm.—
			7 min.	0.97	7.36								6 min.	1.00	8.44
			14 min.	0.84	1.31								12 min.	1.00	5.72
			24 min.	0.77	1.08								23 min.	0.91	1.40
			34 min.	0.76	1.08								33 min.	0.85	2.07
			44 min.	0.77	0.97								51 min.	0.87	1.17
			54 min.	0.76	1.14								58 min.	0.89	1.25

Atr.: Atropine sulfate subcut. Urg.: Urginin. Dig.: Digitalis Folia. R-R Int.: average ventricular cycle. C.S.P.: Carotid Sinus Pressure.

The functional classification of the cases was made according to the Standard Nomenclature of The American Heart Association.

RESULTS

The response of the eight patients to carotid sinus stimulation after the administration of atropine was ascertained on twenty-one occasions. The observations on three patients do not appear in Table II because they were unwilling to cooperate throughout the study. On sixteen occasions a transient increase in the response to sinus stimulation was demonstrated. The augmented response was present five to twelve minutes after atropine was injected subcutaneously. No attempt was made to ascertain the time of onset or total duration of this initial stage. There was a variable degree of paresis of the carotid sinus reflex in all of the patients for the remainder of the experimental period, which lasted forty-seven to seventy minutes after the injection. These effects are illustrated in Fig. 1.

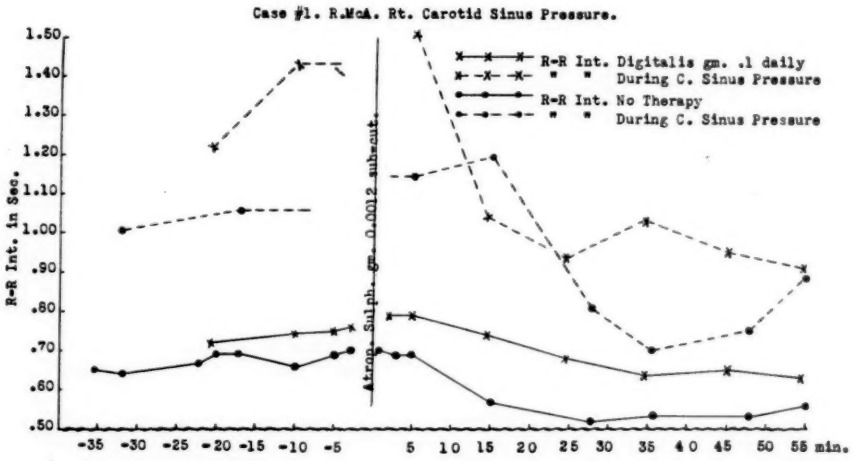

Fig. 1.—Case 1. R. McA. Effect of atropine on the results of carotid sinus pressure. Ordinates: minutes before and after subcut. injection of atropine sulfate. Abscissae: duration of average ventricular cycle in seconds. The upper two curves represent the R-R values with carotid sinus pressure; the lower two curves are the control ventricular rates immediately preceding sinus pressure.

The relative influence of digitalis, urginin, and congestive failure on carotid sinus stimulation was ascertained in the following cases:

Case 1.—R. McA., a white man, 60 years of age, was admitted to St. Luke's Hospital Dec. 16, 1936; he was in acute respiratory distress, and had pink, frothy sputum. Shortness of breath on exertion had been present for the preceding six weeks. He was discharged improved. Thereafter his physical condition was variable; occasionally he was able to do heavy work as a stonemason. Severe dizziness was sometimes present. During this period of relatively good health the standard observations on the results of stimulation of the carotid sinus were begun. The observations were continued throughout subsequent visits, when his circulatory status fluctuated greatly. Moderate congestive failure was precipitated by a mild rhinitis in December, 1939. He was admitted to the hospital Jan. 17, 1940, and discharged

greatly improved on Feb. 3, 1940. Two weeks later he returned with a severe respiratory infection and generalized edema. A pneumococcus (Type XV) was identified in the sputum. Although the pulmonary infection improved as the result of sulfapyridine therapy, the patient died on March 8, 1940, of congestive cardiac failure, with marked azotemia. At post-mortem examination the heart weighed 530 Gm.; there were thickening of the endocardium of the left atrium, mild fibrous changes in the triscuspid valve, and a bicuspid aortic valve, with calcification of the leaflets. The lungs showed moderate pneumoconiosis, with emphysematous blebs and multiple, small infarctions.

The results of stimulating the carotid sinus in Case 1 are illustrated in Fig. 2. On seven occasions the functional classification was I, and, during six of these periods, sinus pressure resulted only in slowing of the ventricles. Myocardial insufficiency was present at the time of the remaining observations, and in all of these ventricular standstill was induced. The patient was taking digitalis on four occasions and urginin on two others, but ventricular standstill was produced by sinus stimulation on only three occasions.

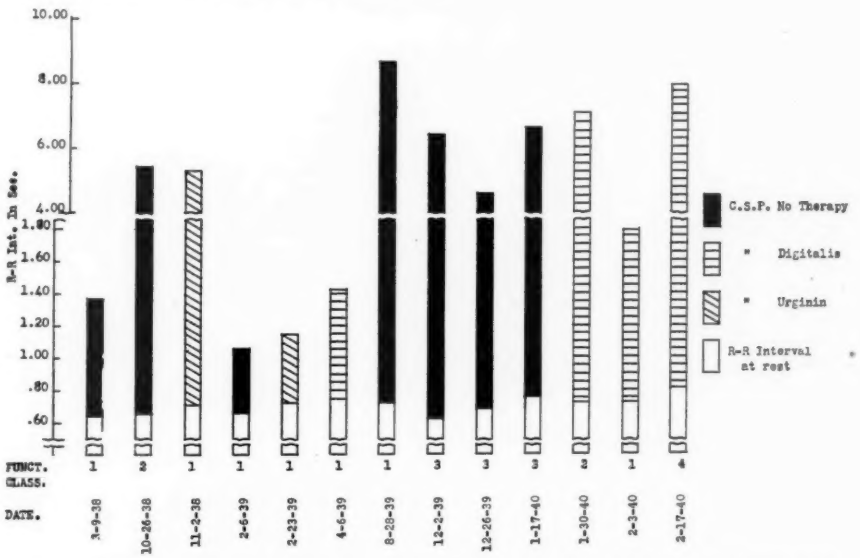

Fig. 2.—Case 1. R. McA. Effect of carotid sinus pressure on the ventricular rate. Abscissae: average ventricular cycle in seconds. FUNCT. CLASS.: functional classification according to American Heart Association. C.S.P.: average R-R intervals with carotid sinus pressure. R-R interval at rest: control ventricular rate immediately preceding carotid sinus stimulation. The symbols in the remaining charts are similar.

The longest period of ventricular standstill occurred Aug. 28, 1939, when the functional classification was I. This result is unexplained. The symptoms produced by carotid sinus pressure showed a marked variation. On Aug. 28, 1939, stimulation resulted in transient syncope, hyperpnea (++), and clonic movements of the arms. On Feb. 17, 1940, when Class IV congestive failure was present, stimulation resulted in opisthotonos with generalized clonic movements (++++), hyperpnea (++++), marked pallor of the skin, a sustained fall in blood pressure, and involuntary micturition. When the patient had acute pulmonary edema, standstill of the heart, with syncope, was produced by slight pressure on the neck.

Case 2.—F. S., a white man, 54 years of age, was seen in the Outpatient Department on Feb. 17, 1937. He was short of breath on exertion, and had occasional attacks of paroxysmal nocturnal orthopnea and swelling of the legs. He had ex-

perienced frequent, severe attacks of dizziness for a year. There was a history of multiple attacks of acute migratory polyarthritis in childhood, and of a penile chancre at the age of 19 years. His blood Wassermann and Kline reactions were strongly positive. Sugar was present in the urine, and a glucose tolerance test showed prolonged hyperglycemia. The diagnoses were rheumatic heart disease, with mitral and aortic stenosis, latent syphilis, and mild diabetes mellitus. The latter condition was controlled by diet and infrequent, small doses of insulin. Adequate antisyphilitic therapy was given, and the standard observations on the carotid sinus reflex were begun on March 12, 1938. His condition has been variable, but the patient has remained cooperative and cheerful, and continues to attempt to be self sufficient. The dizziness is still present, but is less severe than when he was first examined.

Twenty-one observations in Case 2 are recorded in Fig. 3. Arbitrarily, for the purpose of discussion, the carotid sinus was considered to be hyperactive in this case when stimulation of the sinus produced a ventricular pause of more than 7.5 seconds. This occurred fourteen times, and the functional classification on thirteen of these occasions was III. The patient was receiving a cardiotonic drug when fourteen of the observations were made, but on six of these occasions stimulation did not produce ventricular standstill for 7.5 seconds. When the patient was receiving no medication, but was in Class III (six times), sinus massage uniformly produced prolonged standstill of the ventricles. When he was in Class II (eight times), such an effect was secured only once, although he was taking digitalis on seven of these occasions. The carotid sinus reflex in this case was apparently more sensitive when circulatory insufficiency was marked (Class III) than when a therapeutic concentration of either digitalis or urginin was present.

In an attempt to test the above inference, the periods of prolonged ventricular standstill when Class III congestive failure was present were analyzed statistically. The mean of the ventricular pauses when he was receiving no drug was 12.32 seconds, and the mean of the pauses was 11.19 seconds when he was taking digitalis or urginin. The difference of the means is 1.13, and the standard error of the difference is 1.16, so that the difference is not significant.

On Feb. 17, 1939, two trials of carotid sinus pressure resulted in average ventricular cycles of 1.12 and 1.14 seconds. We are reasonably certain that the sinus reflex was not hyperactive on that date. The patient's condition was good at this time and he was taking no drugs.

Case 3.—A. G., a colored man, 66 years of age, was brought to St. Luke's Hospital Dec. 27, 1936, by police ambulance after he had fallen unconscious on the street. There was a long history of repeated syncope, with frequent attacks of severe dizziness, for the preceding three years. The diagnoses were syphilitic aortitis, myocardial hypertrophy with circulatory insufficiency, and carotid sinus syndrome. His respiratory distress diminished after antisyphilitic therapy, but he was usually short of breath after moderate exertion. The syncopal attacks did not recur, but the patient attributed their absence to his physical inactivity. This sedentary life was necessitated by severe dizziness which was precipitated by movements of the neck. Stripping operations on the carotid arteries were done separately in October and November, 1937. A carotid body was histologically identified in material obtained from the right artery. Thereafter he had no recurrence of his "spells," although the ventricular rate was always slowed by pressure over the bifurcation of the right carotid artery. These results were in distinct contrast to those obtained preoperatively, when carotid sinus stimulation, although very slight, usually produced ventricular standstill, with syncope and convulsive movements. The standard observations on the results of carotid sinus stimulation were begun April 9, 1938, and continued to July 29, 1941. During this period there were times when minimal degrees of congestive failure were present.

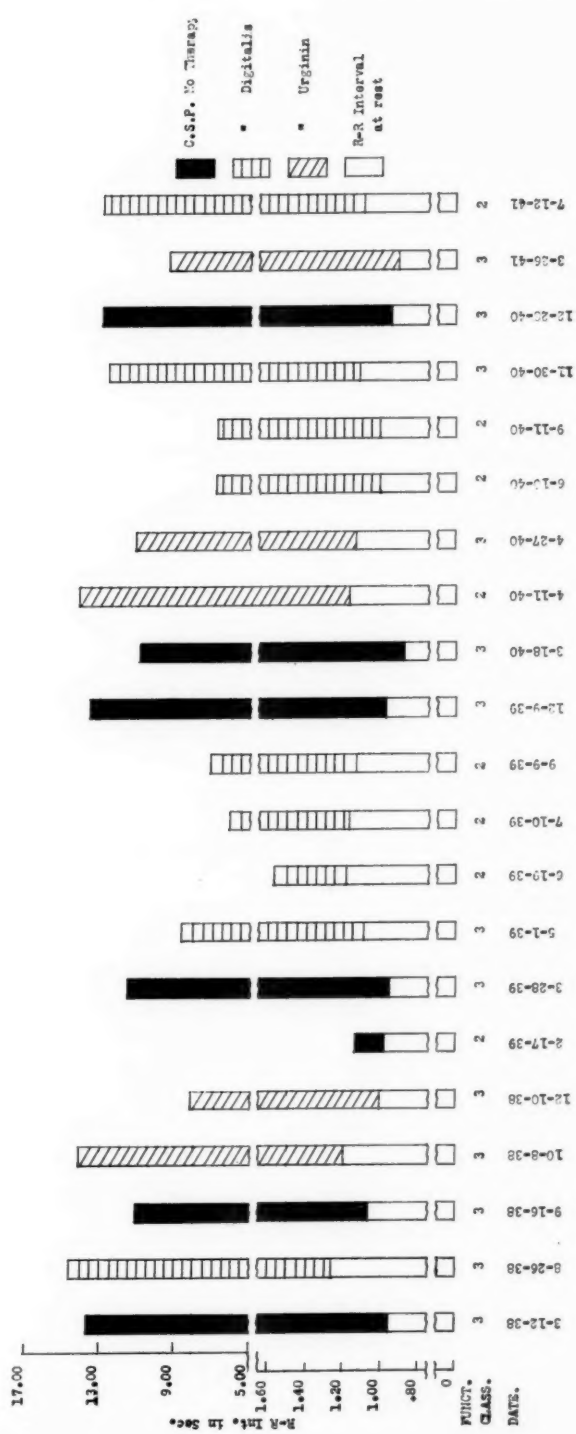

Fig. 3.—Case 2. F. S. Effect of carotid sinus pressure on the ventricular rate. (Symbols as in Fig. 2.)

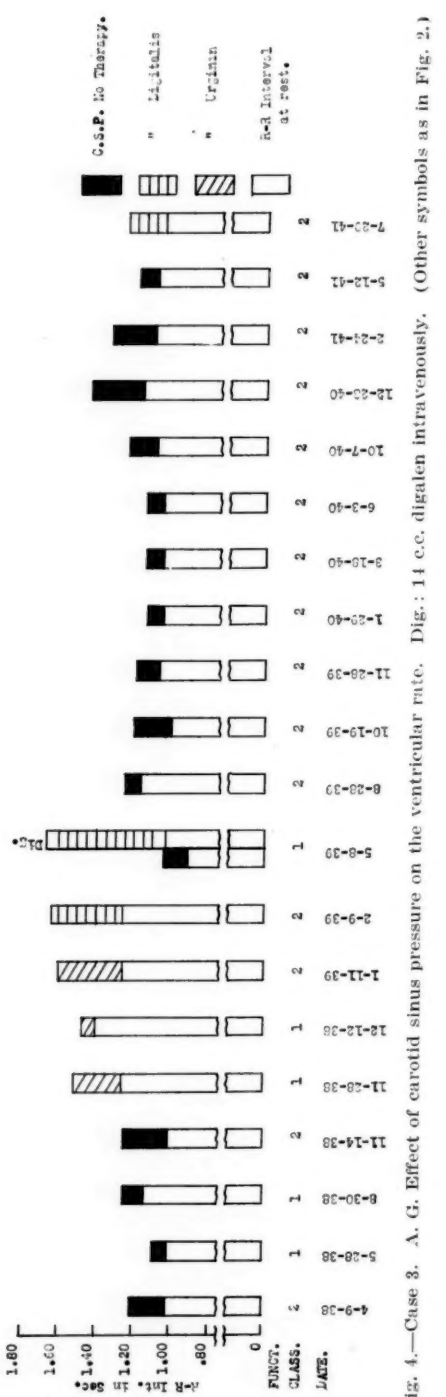

Fig. 4.—Case 3. A. G. Effect of carotid sinus pressure on the ventricular rate. Dig.: 14 c.c. digalen intravenously. (Other symbols as in Fig. 2.)

The average duration of the ventricular cycle after stimulation of the carotid sinus on twenty-one occasions is shown by Fig. 4. The sensitizing effect of digitalis and urginin seems apparent. Statistical analysis of the results shows that the difference is significant. The mean of six pressures when the patient was receiving digitalis or urginin was 1.51 seconds, and the mean of the control group was 1.26 seconds. The difference of the means is 0.307, and the standard error of the difference is 0.0549.

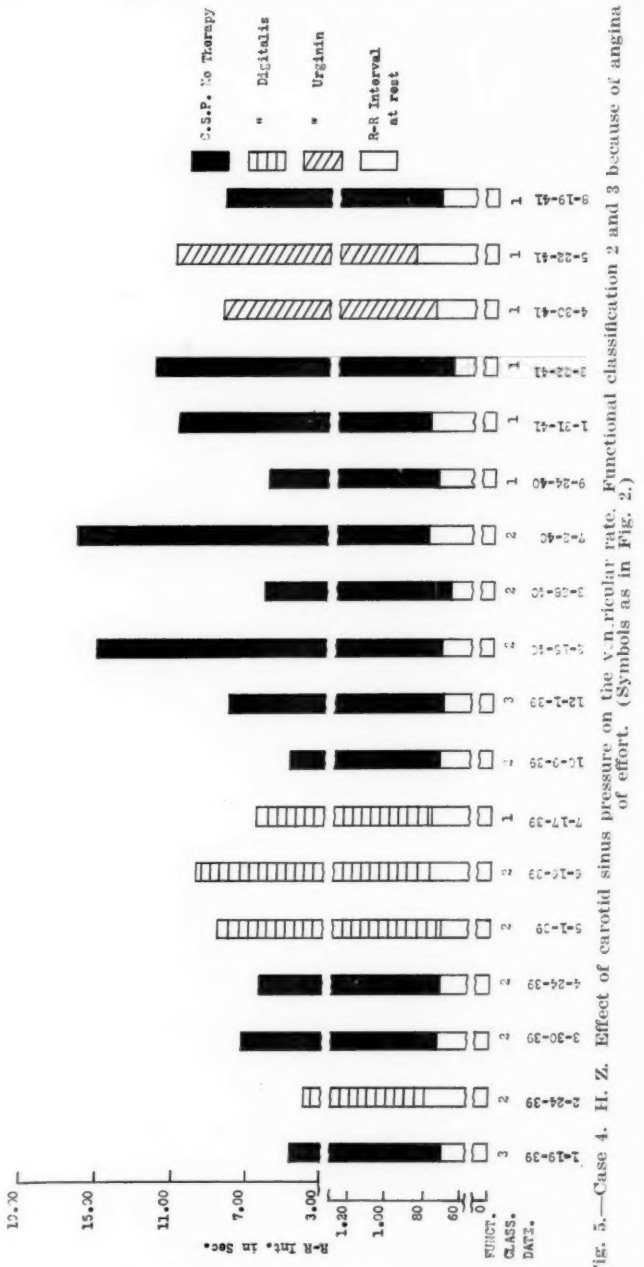

Fig. 5.—Case 4. H. Z. Effect of carotid sinus pressure on the ventricular rate. Functional classification 2 and 3 because of angina of effort. (Symbols as in Fig. 2.)

On May 8, 1939, the maximum ventricular cycle without stimulation was 0.92 second, and during carotid sinus pressure the maximum average cycle was 1.04 seconds. A moderate dose of digalen (14 c.c.) was given intravenously, and seventy-two minutes later the maximum average cycle was 1.03 seconds; with carotid sinus stimulation the average ventricular cycle increased to 1.66 seconds.

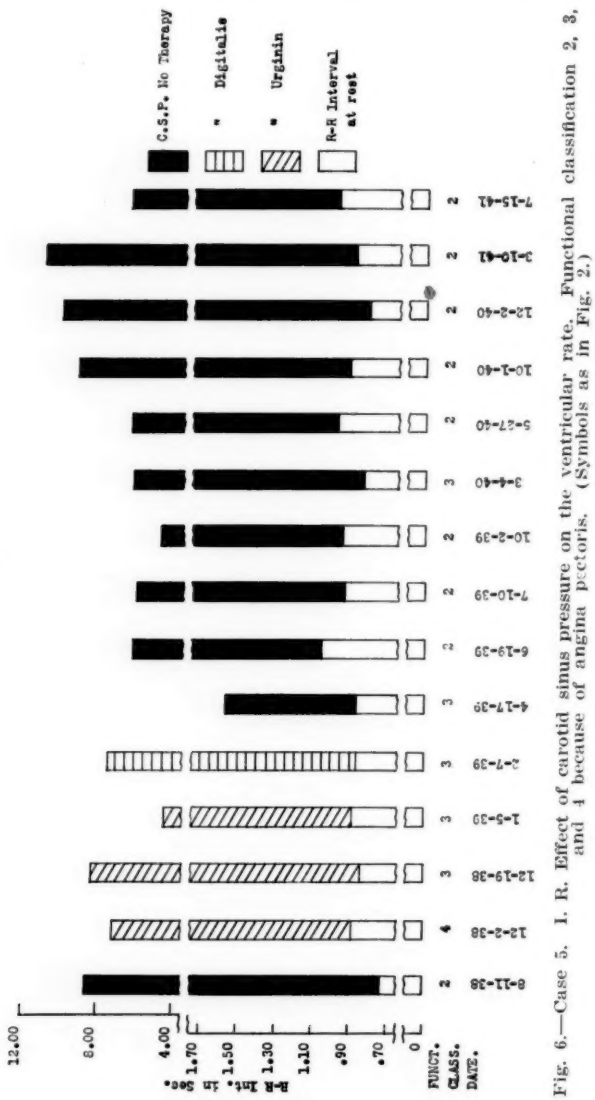

Fig. 6.—Case 5. I. R. Effect of carotid sinus pressure on the ventricular rate. Functional classification 2, 3, and 4 because of angina pectoris. (Symbols as in Fig. 2.)

Case 4.—H. Z., a white man, 44 years of age, was admitted to the hospital July 31, 1937, with severe, persistent precordial pain. He had experienced repeated attacks of dizziness for two years, and had fallen to the floor unconscious on several occasions. The diagnoses were acute myocardial infarction, diabetes mellitus, and carotid sinus syndrome. The carotid sinus was stimulated on numerous occasions, and the standard observations were made between Jan. 19, 1939, and Aug. 19, 1941. The diabetes was of moderate severity, and recurring anginal discomfort

was occasionally present. The only possible evidence of congestive failure was a variation of the breath sounds at the extreme bases of the lungs posteriorly on several occasions.

Fig. 5 shows the cycle lengths during stimulation of the carotid sinus on eighteen separate occasions. On four occasions the patient was receiving digitalis, and, on two others, urginin, but there is no evidence that the carotid sinus had been sensitized by either of these drugs. The variability of the results is noteworthy, although the carotid sinus was extremely hyperactive on several occasions.

Case 5.—I. R., a white man, 54 years of age, was admitted to the hospital Nov. 20, 1937, because of acute myocardial infarction complicated by pulmonary infarction. He was discharged Nov. 13, 1938, and remained under observation thereafter. His general condition has been satisfactory, although his activities have been restricted because of respiratory distress and attacks of angina pectoris. A few spontaneous syncopal attacks have occurred, and attacks of dizziness have been frequent, but not severe.

The effects of carotid sinus pressure on fifteen occasions are shown in Fig. 6. Urginin was given for three periods, and digitalis for one. We are unable to correlate the varying results of sinus stimulation with any of the factors under consideration in the present communication.

An analysis of the data in these five cases showed no apparent difference in the sensitizing effects of digitalis and urginin in small doses (Figs. 2-6). Therefore, we believe that these two drugs, when given in small doses, have relatively the same influence on the hyperactive carotid sinus reflex.

DISCUSSION

The activity of the carotid sinus reflex cannot be absolutely reflected by the change in ventricular rate which results from its stimulation, for the efferent paths of the reflex are are complex and show individual variations.[6, 7] However, ventricular cycles can be accurately measured and control of the heart rate is one of the major functions of the carotid sinus.[24] In addition, the ventricular cycles in our cases definitely tended to become longer as the intensity of the induced syncopal states increased.

The results of the atropine experiments seem to be conclusive, and might have been anticipated, for previous reports had clearly indicated their probability. The observations show that the effect of carotid sinus stimulation on the heart rate is first increased and then decreased by the subcutaneous injection of atropine sulfate. The early effect (greater slowing of the heart) seems to be merely an exaggeration of the initial vagotonia which is exhibited by the vagus after the administration of atropine.

Our observations are in accord with previous statements that congestive cardiac failure increases the activity of the carotid sinus. Congestive failure was the only factor in Cases 1 and 2 which was constantly associated with prolonged ventricular standstill and with an increase in severity of symptoms after sinus massage. Therefore, we believe that myocardial insufficiency was the major factor in the carotid sinus syndrome in these two cases. It is improbable that such a change would occur so regularly unless a causal relationship existed. Our observations

indicate that the decrease in the sensitivity of the carotid sinus reflex which results from improvement of the circulation in such cases will exceed any vagotonia produced by small doses of digitalis.

We doubt that digitalis may be responsible for sudden death in patients with a hyperactive carotid sinus reflex. Nevertheless, large doses of this drug result in an increased activity of the carotid sinus reflex before improvement in the circulation occurs. Therefore, we elected to digitalize our patients with small doses,[25] and we believe that they received sufficient amounts of the drugs. In Case 1 the dose of digitalis was temporarily increased, with moderate toxic effects, but with no further improvement in the circulation. Although small doses were constantly used in Case 2, mild toxic symptoms were produced occasionally, and the respiratory distress and peripheral edema were greatly alleviated.*

The sensitivity of the carotid sinus reflex was demonstrably increased by small doses of digitalis in Case 3. In this instance, carotid sinus pressure resulted in a slowing of the heart rate after the administration of 0.2 Gm. (gr. iii) of digitalis folia or of 1.0 to 2.0 mg. of Urginin daily. Increased sensitivity of the sinus was produced promptly in this case by giving a moderate dose (14 c.c.) of digalen intravenously. The results of sinus massage were so variable in Cases 4 and 5 that the sensitizing effect of digitalis was not apparent. Only minor electrocardiographic changes occurred after the administration of digitalis, and congestive failure was never present in these two cases.

Throughout these observations there were occasional, spontaneous variations in the activity of the carotid sinus reflex, and, on one occasion (Case 1), sinus stimulation resulted in unexplained, prolonged ventricular standstill, although the patient was not taking digitalis or urginin, and the circulation was adequate. We believe that such spontaneous changes had little influence on the results obtained from stimulation of the carotid sinus in our cases.

CONCLUSIONS

In our cases, both congestive cardiac failure and digitalis increased the activity of the carotid sinus reflex, but congestive failure was a more potent factor than small doses of digitalis.

Hyperactivity of the carotid sinus reflex is no contraindication to the use of digitalis in the treatment of congestive cardiac failure.

Digitalis and urginin, when given in small doses, have similar effects on the hyperactive carotid sinus reflex.

Therapeutic doses of atropine, given subcutaneously, have the following effect on the results of carotid sinus stimulation: after the injection of atropine, stimulation of the carotid sinus will produce a

*The improvement in the circulation in these cases after the use of digitalis is of additional interest. Previous to the administration of digitalis, significant degrees of congestive failure were sometimes present, although the heart rate was slow and the vagus tone was apparently increased. Presumably, this increased vagotonia was sometimes so marked that it resulted in cardiac standstill and syncope. Similar observations have been made previously.[26]

greater slowing of the heart; this phase of atropine action will be followed by a period of vagal paresis, during which stimulation of the carotid sinus has a lessened effect on the heart rate.

REFERENCES

1. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefaesse, Dresden, 1927, Theodor Steinkopff.
2. Heyman, C.: The Pressoreceptive Mechanism for the Regulation of Heart Rate, Vasomotor Tone, Blood Pressure and Blood Supply, N. England J. Med. **219**: 147, 1938.
3. Koch, E.: Klinische Beobachtungen zum Karotisdruckversuch, München. med. Wchnschr. **70**: 1316, 1923.
4. Budda, M.: Chirurgische Erfahrungen über die Karotissinusdruckversuch, Ztschr. f. d. ges. exper. Med. **50**: 207, 1926.
5. Anrep, G. V.: The Proprioceptive Mechanism of Cardiovascular Regulation, Lane Medical Lectures, Stanford University Press, 1936.
6. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease, Medicine **12**: 297, 1933.
7. Ferris, E. B., Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, Medicine **14**: 377, 1935.
8. Nathanson, M. H.: Further Observations on the Effect of Drugs on Induced Cardiac Standstill; Effect of Epinephrine and Related Compounds, Arch. Int. Med. **54**: 111, 1934.
9. Radnai, P., and Mosonyi, L.: Die Bedeutung der Reflexerregbarkeit des Vagus bei Angina Pectoris, Klin. Wchnschr. **16**: 228, 1937.
10. Sigler, L. H.: Hyperactive Cardioinhibitory Carotid Sinus: A Possible Aid in the Diagnosis of Coronary Disease, Arch. Int. Med. **67**: 177, 1941.
11. Levine, S. A., Ernstene, A. C., and Jacobson, B. M.: The Use of Epinephrine as a Diagnostic Test for Angina Pectoris, Arch. Int. Med. **45**: 191, 1930.
12. Cottrel, J. E., and Wood, F. C.: The Effect of Epinephrine in Angina Pectoris, Am. J. M. Sc. **181**: 36, 1931.
13. Katz, L. N., Hamburger, W. W., and Lea, M.: The Diagnostic Value of Epinephrine in Angina Pectoris, AM. HEART J. **7**: 371, 1932.
14. v. Anrep, B.: Ueber chronische Atropinvergiftung, Arch. f. d. ges. Physiol. **21**: 185, 1880.
15. Mueller, E.: Ueber die Wirkung des Atropins auf das gesunde und kranke menschliche Herz, 8.° Dorpat, 1891.
16. Petzetakis, M.: La Phase Stimulatrice De L'Atropine, Presse méd. 548, 1916.
17. Halsey, J. T.: The Digitalized Dog's Heart as Affected by Amyl Nitrate and Atropine, J. Exper. Med. **25**: 729, 1917.
18. Lewis, T., Drury, A. N., and Iliescu, C. C.: Some Observations Upon Atropine and Strophanthus, Heart **9**: 21, 1922.
19. Lewis, T., Drury, A. N., Wedd, A. N., and Iliescu, C. C.: Upon Fibrillation of the Auricles, Heart **9**: 207, 1922.
20. Rudolph, R. D., and Bulmer, F. D. R.: Some Cardiac Effects of Atropine, Am. J. M. Sc. **168**: 641, 1924.
21. McGuigan, H.: The Effect of Small Doses of Atropine Upon the Heart Rate, J. A. M. A. **76**: 1338, 1921.
22. Carr, J. G., and Mayer, J. D.: Clinical Experience With a Derivative of Squill, Arch. Int. Med. **56**: 700, 1935.
23. Chamberlin, F. F., and Levy, R. L.: Clinical Study of a Preparation of Squill (Urginin), AM. HEART J. **14**: 268, 1937.
24. Winder, C. V.: Quantitative Observations on the Extravagal Component of the Carotid Sinus, Am. J. Physiol. **124**: 421, 1938.
25. Otto, H. L., Gold, H., and Messeloff, C. R.: Studies on Digitalis in Ambulatory Patients With Cardiac Disease, Arch. Int. Med. **52**: 725, 1933.
26. Wenckebach, K. F., and Mackenzie, J.: Discussion on the Effect of Digitalis on the Human Heart, Brit. Med. J. **2**: 1600, 1910.

THE EFFECT OF QUINIDINE UPON SINUS TACHYCARDIA, INCLUDING THE PRODUCTION OF TRANSIENT BUNDLE BRANCH BLOCK

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THE observations to be described in this paper were made in connection with a study of auricular paroxysmal tachycardia. It is well known that quinidine frequently slows the cardiac rate in auricular paroxysmal tachycardia, and sometimes stops the paroxysm. The same effects may be produced by quinine, and the actions of these two drugs are, no doubt, similar. Singer and Winterberg[1] have shown that in sinus tachycardia quinine either does not alter the heart rate or increases it somewhat. It seemed desirable to investigate the effect of quinidine in sinus tachycardia.

A single dose of 0.6 Gm. of quinidine sulfate was given by mouth to each of five patients with sinus tachycardia. Four of the patients had exophthalmic goiter, and the fifth had chronic ulcerative colitis with fever and anemia. In all five cases the heart was organically sound, and none of the patients was receiving any drug which might affect the heart. The heart rate was counted at intervals before, and for at least two hours after, giving the quinidine, and electrocardiograms were likewise taken before giving the quinidine and two hours later.

The effect of quinidine upon the heart rate is shown in Table I. The rate was not affected or was slightly increased. These observations are similar to those of Singer and Winterberg,[1] who used quinine. They show that quinidine does not slow the rate of impulse formation in the sinoauricular node.

The electrocardiograms showed, in some instances, slight changes in the T waves after the administration of quinidine. With one exception, however, there were no significant alterations in the P-R or QRS intervals.

The one exception was Case 5, in which there was transient right bundle branch block two hours after the administration of the quinidine. Electrocardiograms taken a few minutes before the quinidine was given, and again on the following day, were essentially normal (Fig. 1). Multiple precordial leads showed relatively late activation of the right ventricle at the time when the bundle branch block was present. Two weeks later, 0.6 Gm. of quinidine sulfate was again given by mouth,

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TABLE I

THE EFFECT OF QUINIDINE BY MOUTH UPON THE HEART RATE IN SINUS TACHYCARDIA

CASE 1		CASE 2		CASE 3		CASE 4		CASE 5			
TIME	RATE	TIME	RATE	TIME	RATE	TIME	RATE	TIME	RATE	TIME	RATE
12/15/41		2/ 7/41		3/ 6/41		11/12/41		2/ 7/41		2/21/41	
11:00 a.m.	156	1:00 p.m.	108	4:00 p.m.	120	1:45 p.m.	150	1:00 p.m.	90	1:30 p.m.	108
11:15	147	1:15	110	4:01	Quinidine	2:20	142	1:15	110	1:35	94
2:30 p.m.	Quinidine	1:35	124		0.2 Gm.	2:23	136	1:35	108	1:45	Quinidine
	0.2 Gm.	1:45	112		(test dose)	2:25	Quinidine	1:45	110		0.6 Gm.
	(test dose)	2:15	115	5:00	108		0.6 Gm.	1:55	107	2:45	130
12/16/41		2:20	Quinidine	3/ 7/41		3:00	140	2:00	Quinidine	3:45	130
9:20 a.m.	143		0.6 Gm.	8:55 a.m.	108	3:25	143		0.6 Gm.	3:50	136
9:25	150	2:35	110	9:45	100	3:55	150	2:40	106	2/22/41	
9:30	Quinidine	3:00	104	9:55	107	4:25	141	3:00	106	10:45 a.m.	115
	0.6 Gm.	3:30	108	10:00	Quinidine	11/13/41		3:30	113		
10:45	150	4:00	108		0.6 Gm.	11:15 a.m.	120	4:00	118		
11:30	144	4:15	115	11:00	128			4:05	109		
		5:15	124	12:00	107			5:15	100		
				1:00 p.m.	136			2/ 8/41			
								12:05 p.m.	88		

and two hours later the electrocardiogram again showed transient right bundle branch block (Fig. 2). Multiple precordial leads again showed relatively late activation of the right ventricle at the time when the bundle branch block was present. This observation is of interest in connection with the interpretation of the aberrant ventricular deflections which are sometimes observed after the administration of quinidine to patients with auricular fibrillation.

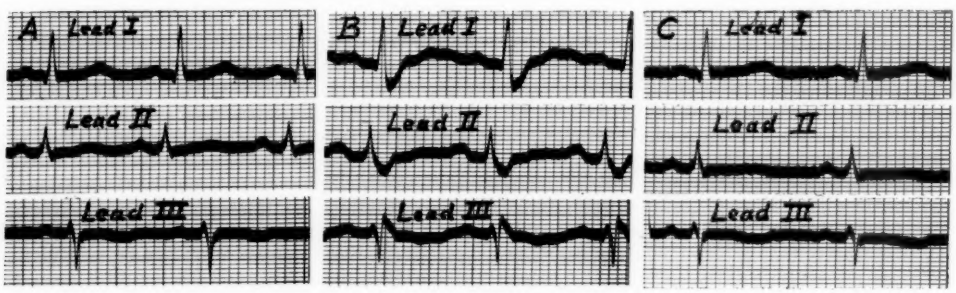

Fig. 1.—Quinidine sulfate, 0.6 Gm., by mouth at 2:00 P.M. *A*, Control curve, 1:55 P.M. *B*, Right bundle branch block, 4:05 P.M. *C*, The following day, 12:05 P.M.

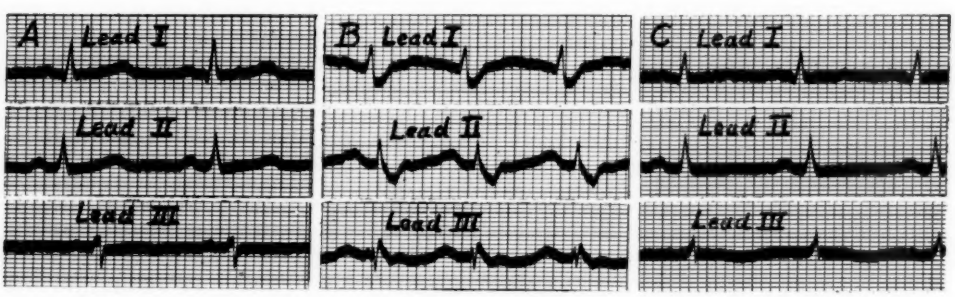

Fig. 2.—Two weeks after Fig. 1. Quinidine sulfate, 0.6 Gm., by mouth at 1:45 P.M. *A*, Control curve, 1:35 P.M. *B*, Right bundle branch block, 3:50 P.M. *C*, The following day, 10:45 A.M.

When quinidine is administered in the treatment of auricular fibrillation, and its effects followed closely by means of frequent electrocardiograms, approximately one-third of the patients show abnormal QRS deflections.[2, 3] These resemble the abnormal complexes of ectopic ventricular beats or of defective intraventricular conduction. They occur at the height of the quinidine effect, and disappear shortly after the quinidine has been stopped.

It has been abundantly demonstrated that quinidine depresses intraventricular conduction, as shown by prolongation of the QRS interval,[3-9] and the abnormal QRS complexes which follow quinidine have been attributed by some observers to defective intraventricular conduction.[3, 5, 7, 9] Furthermore, it is well known that quinidine may abolish ectopic ventricular beats, and that it is especially effective in stopping

ventricular paroxysmal tachycardia.[10, 11, 12] Nevertheless, the abnormal QRS deflections which follow quinidine have been attributed by some observers to ectopic ventricular beats.[2, 6, 10, 13]

In auricular fibrillation, quinidine almost invariably causes an increase in ventricular rate. This makes it specially difficult to distinguish between abnormal deflections caused by ectopic premature ventricular beats, occurring singly or in runs, and those caused by defective intraventricular conduction, which would be especially likely to appear at higher rates or after the shorter diastoles. Lewis and his associates[2] have pointed out that there should be a close relation between prematurity and abnormality of ventricular deflections, if the abnormality were the result of impaired conductivity. They recognized that, in a general way, such a relationship existed, but did not consider it sufficiently close to indicate impaired intraventricular conductivity. In published electrocardiograms showing abnormal ventricular deflections which are attributed to ectopic ventricular beats caused by quinidine, alternative interpretations are possible, namely, that the ectopic beats occurred spontaneously or for some other reason, and were not caused by quinidine, or that the deflections were aberrant because of impaired intraventricular conductivity.[6, 14]

White, Marvin, and Burwell[5] mentioned a case in which quinidine produced marked intraventricular block without abolishing the auricular fibrillation. Korns[7] published curves from a patient who showed bundle branch block after 6 grams of quinidine, which disappeared shortly after withdrawal of the drug; auricular fibrillation was present and the ventricular rate was 90 per minute, both in the presence of the bundle branch block and in its absence. Wilson, Wishart, Clark, and Herrmann[3] described a case of auricular fibrillation in which all of the ventricular deflections became abnormal after 1.6 Gm. of quinidine. Normal rhythm returned two hours later, and all of the ventricular deflections were still abnormal; the normal type returned, however, as soon as the quinidine effect passed off. The abnormal deflections were attributed to impaired intraventricular conductivity.

In the present case, the aberrant ventricular deflections were clearly the result of impaired intraventricular conductivity caused by quinidine. It is our opinion that when quinidine causes abnormal QRS deflections, it does so by depressing conduction within the ventricles.

SUMMARY

A single dose of 0.6 Gm. of quinidine sulfate was given by mouth to each of five patients with sinus tachycardia. The cardiac rate was either not affected or was slightly increased.

In one patient, transient right bundle branch block occurred two hours after the administration of quinidine, upon two separate occasions.

When quinidine causes abnormal QRS deflections, it does so by depressing conduction within the ventricles.

REFERENCES

1. Singer, R., and Winterberg, H.: Chinin als Herz-und Gefässmittel, Wien. Arch. f. inn. Med. **3**: 329, 1922.
2. Lewis, T., Drury, A. N., Wedd, A. M., and Iliescu, C. C.: Observations Upon the Actions of Certain Drugs Upon Fibrillation of the Auricles, Heart **9**: 207, 1922.
3. Wilson, F. N., Wishart, S. W., Clark, N. F., and Herrmann, G. R.: Nature of Abnormal Ventricular Complexes During Quinidine Treatment of Auricular Fibrillation, Proc. Soc. Exper. Biol. & Med. **23**: 273, 1926.
4. Lewis, T., Drury, A. N., Iliescu, C. C., and Wedd, A. M.: Observations Relating to the Action of Quinidine Upon the Dog's Heart; With Special Reference to Its Action on Clinical Fibrillation of the Auricles, Heart **9**: 55, 1921.
5. White, P. D., Marvin, H. M., and Burwell, C. S.: The Action of Quinidine Sulphate in Heart Disease, to Abolish the Circus Movement of Auricular Flutter and Fibrillation, Boston M. & S. J. **185**: 647, 1921.
6. Levy, R. L.: Clinical Studies of Quinidine. II. Alterations in the Cardiac Mechanism After Administration of Quinidine to Patients With Auricular Fibrillation With Consideration of Certain Toxic Effects of the Drug, Arch. Int. Med. **30**: 451, 1922.
7. Korns, H. M.: An Experimental and Clinical Study of Quinidine Sulphate, Arch. Int. Med. **31**: 15, 1923.
8. Gold, H., and Modall, W.: The Action of Quinidine on the Heart in the Normal Unanesthetized Dog, J. Pharmacol. & Exper. Therap. **46**: 357, 1932.
9. Gold, H., and Otto, H. L.: The Use of Quinidine in Ambulatory Patients for the Prevention of Paroxysms of Auricular Flutter and Fibrillation; With Especial Reference to Dosage and the Effects Upon Intraventricular Conduction, AM. HEART J. **9**: 219, 1933.
10. Hepburn, J., and Rykert, H. E.: The Use of Quinidine Sulfate Intravenously in Ventricular Tachycardia, AM. HEART J. **14**: 620, 1937.
11. Cohn, A. E., and Levy, R. L.: Experimental Studies of the Pharmacology of Quinidine, Proc. Soc. Exper. Biol. & Med. **18**: 283, 1921.
12. Wilson, F. N., Wishart, S. W., Macleod, A. G., and Barker, P. S.: A Clinical Type of Paroxysmal Tachycardia of Ventricular Origin in Which Paroxysms are Inducted by Exertion, AM. HEART J. **8**: 155, 1932.
13. Maynard, E. P.: Five Years' Experience in the Treatment of Chronic Auricular Fibrillation With Quinidine, Am. J. M. Sc. **175**: 55, 1938.
14. Jezer, A., and Schwartz, S. P.: Unusual Manifestations Following the Use of Quinidine Sulphate in a Patient With Auricular Flutter, AM. HEART J. **10**: 124, 1934.

AURICULAR PAROXYSMAL TACHYCARDIA WITH AURICULOVENTRICULAR BLOCK

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AURICULAR paroxysmal tachycardia is a condition in which the heart beats rapidly and regularly in response to impulses arising in the auricles. The attacks are characterized by abrupt transitions, from normal rhythm to tachycardia at their onset, and from tachycardia to normal rhythm at their termination. They usually last a few minutes or a few hours, rarely much longer. The rate is usually between 150 and 220 per minute, commonly near 200. The ventricles respond, as a rule, to each auricular beat. The attacks can often be stopped by pressure upon the carotid sinus, or by large doses of digitalis, less commonly by quinidine. The precise mechanism of the auricular tachycardia is not understood. It is commonly believed that a rapid succession of impulses arises from an ectopic focus in the auricles. It is possible that in some manner each beat initiates the succeeding beat, or that the tachycardia depends upon the establishment of a circus rhythm in the auricular muscle. This last possibility has been discussed in considerable detail by Lewis.[1] It is of interest that auricular paroxysmal tachycardia seldom occurs in patients who have had previous attacks of auricular flutter or fibrillation, and that these disturbances, which are caused by circus rhythm, are uncommon in patients who have had auricular paroxysmal tachycardia.

In auricular flutter the auricular activity is characterized by a high degree of regularity and uniformity. The auricular rate is usually between 240 and 375 per minute. The ventricles very rarely respond to each auricular impulse; there is nearly always partial atrioventricular block, commonly 2:1. The abnormal mechanism is usually more persistent than auricular paroxysmal tachycardia, and often lasts for weeks or months, but repeated short attacks sometimes occur. Carotid sinus pressure slows the ventricles but does not alter the auricular mechanism. Digitalis slows the ventricles, and, when large amounts are given, usually converts auricular flutter into auricular fibrillation. Quinidine always slows the auricular rate, but does not often restore normal rhythm.

In rare instances of auricular paroxysmal tachycardia, the ventricles do not respond to each auricular beat in the usual manner. There may

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TABLE

AURICULAR PAROXYSMAL TACHYCARDIA

	AUTHORS	AGE	SEX	DURATION OF SYMPTOMS	FREQUENCY OF ATTACKS	DURATION OF ATTACKS	AUR. RATE	DEGREE OF A-V BLOCK	P WAVES*		
									LI	LII	LIII
1.	Koplik, 1917	10	M	2 years			200	2:1 to 3:1			
2.	Singer and Winterberg, 1922	70	M				184	complete		+	
3.	Gallavardin, 1923	60	F	a few hours	one attack	a few hours	180	2:1		+	
4.	Lenhartz and Samet, 1924	29	F	3 years	3 attacks	up to 94 days	196 to 188	2:1	−	+	+
5.	Sprague and White, 1925	48	F	10 years	4 days to 7 months	several hours	190 to 270	2:1	+ +	− +	− +
6.		23	F	6 months	20 attacks	2 hours to 5 days	220	2:1	+	+	+
7.		26	M	10 years	daily to 7 months	a few minutes	166 to 190	2:1		+	
8.	Wenckebach & Winterberg, 1927					several hours	180	3:1 to 6:1			−
9.		20	M	7 weeks	numerous	variable	180	3:2 to 2:1		+	
10.				many years		4 weeks	205	dropped beats	(+, lead not stated)		
11.	Dock, 1928	38	F	22 days	one attack	22 days	186 to 180	2:1 to 4:1	?	∓	∓
12.	Mackinnon, 1934	17	M	at least 5 days	one attack	at least 5 days	121	2:1	(+, lead not stated)		
13.		45	F	2 years	daily	a few minutes	150	dropped beats	(?, lead not stated)		
14.	Brown, 1936	40	F	8 years		a few minutes, persistent	214	2:1	−	+	+
15.	Maddox, 1937	39	F	17 years	2 to 5 years	up to 69 days	120 to 170	1:1 to 3:1	+	−	−
16.	Maarssø, 1937	8	M	1 year		1 month	182 to 160	dropped beats, 2:1	?	?	∓
17.	Fine and Miller, 1940	16	F	several years	daily	brief	120 to 200	dropped beats	−	+	+
18.	Case 1	39	M	9 years	upon exertion	brief	170, 150	1:1 to 3:1		∓	
19.	2	32	M	10 years	daily to several weeks	up to 26 days	200	1:1 to 2:1	+	+	−

*During paroxysmal tachycardia. +, upright; −, inverted; ±, diphasic, upward and then downward; ∓, diphasic, downward and then upward; ?, not visible.

I

WITH AURICULOVENTRICULAR BLOCK

DISABILITY	CONGESTIVE FAILURE	ORGANIC HEART DISEASE	INEFFECTIVE TREATMENT	EFFECTIVE TREATMENT	RESULT	REMARKS
moderate	none	none				electrocardiograms not published
				quinine	stopped the paroxysm	
		syphilitic aortitis			normal rhythm	
marked	none	none	quinine	digitalis and physostigmine	normal rhythm	aur. rate slowed by quinine and by digitalis and physostigmine
moderate	none	none	quinidine	digitalis, removal of cervical ribs	normal rhythm	
moderate	none	none	quinidine	digitalis, rest	normal rhythm	
slight	none	none	quinidine	digitalis	normal rhythm	
				quinine	normal rhythm	
		none			normal rhythm	
				quinine	normal rhythm	
marked	present	mitral stenosis	digitalis		A-V bradycardia	
marked	present	mitral stenosis, aortic regurg.		digitalis	increased block, normal rhythm	
slight	none	mitral lesion		carotid sinus pressure	normal rhythm	probable case. P not identified
marked	acute edema of lungs	mitral and pulmonary lesions or congenital heart		digitalis	normal rhythm	changed to aur. fibr. and then to normal rhythm after digitalis
moderate	none	none	quinine quinidine digitalis acetylcholine	rest	normal rhythm	? sinus tachycardia influenced by rest, exercise, emotion, sleep; auricular rate slowed by digitalis
present	none	enlargement	digitalis			
moderate	none	none	carotid sinus pressure	digitalis, quinidine	normal rhythm	rate influenced by posture
slight	none	none	quinidine	digitalis	increased degree of block	normal rhythm later
marked	none	mitral stenosis	quinidine quinine mecholyl	digitalis, rest	increased degree of block, improved	also auricular flutter and fibrillation

TABLE

	AUTHORS	AGE	SEX	DURATION OF SYMPTOMS	FREQUENCY OF ATTACKS	DURATION OF ATTACKS	AUR. RATE	DEGREE OF A-V BLOCK	P WAVES*		
									LI	LII	LIII
20.	3	41	M	1 year	a few days to 6 months	a few minutes	174 to 218	1:1 to 3:1	+	+	+
21.	4	15	M	3 months	almost continuous	up to 60 days	167 to 129	1:1 to 3:2	?	±	∓
22.	5	62	F	10 months		1 day	167, 158	dropped beats	+	+	+
23.	6	19	M	6 months	upon exertion	at least 13 days	136 to 160	1:1 to 3:1	+	−	−
24.	7	67	M		4 to 14 days	up to 2 days	188 to 235	1:1 to 3:1	?	+	+
25.	8	53	M	2 days	one attack	2 days	188	usually 2:1	?	+	+
26.	9	23	F	6 months	up to 7 days	1 hour to 2 days	195	1:1 to 2:1	+	+	+
27.	10	54	M	4 days	one attack	4 days	200	2:1 or greater	+	+	+
28.	11	52	M	3 days	one attack	3 days	161 to 167	dropped beats	+	+	+
29.	12	80	M	3 days	one attack	3 days	215	usually 4:1	+	+	+
30.	13	68	M	2 days	one attack	2 days	137	2:1	+	+	+
31.	14	17	F	2 days	one attack	2 days	130	dropped beats	+	+	+
32.	15	64	M	9 months	several times daily	a few minutes	192 to 250	2:1 briefly	+	−	−
33.	16	26	F	9 months	9 months		160	complete	+	+	+
34.	17	48	M	3 days	one attack	3 days	180 to 163	2:1	± +	+ +	∓ +
35.	18	45	M	10 days	2 attacks	1 hour and 2 days	212	2:1 to 3:1	+	+	+

*See footnote, p. 766.

be occasional dropped ventricular beats, or 2:1 or higher grades of auriculoventricular block. Auricular paroxysmal tachycardia associated with heartblock differs in several important respects from ordinary paroxysmal tachycardia of auricular origin, and resembles auricular flutter in some particulars. The purpose of this paper is to review seventeen previously reported cases, to present eighteen additional cases, and to describe some of their peculiarities. The important features of these thirty-five cases have been tabulated (Table I).

I—CONT'D

DISABILITY	CONGESTIVE FAILURE	ORGANIC HEART DISEASE	INEFFECTIVE TREATMENT	EFFECTIVE TREATMENT	RESULT	REMARKS
moderate to marked	none	none	quinidine mecholyl	digitalis	increased degree of block	normal rhythm later, aur. rate slowed by quinidine
marked	present	none	quinidine digitalis	none	died 84 days after onset	aur. rate slowed by quinidine. Autopsy
slight	none	none		digitalis	normal rhythm	
moderate to marked	none	? mitral lesion	digitalis mecholyl	quinidine	normal rhythm; died suddenly	aur. rate slowed by quinidine. Autopsy
moderate	none	hypertension, arteriosclerosis, emphysema	digitalis	quinidine	normal rhythm	
incidental	present	right-sided enlargement	digitalis		died	autopsy; bronchiectasis
moderate	none	mitral stenosis, aortic regurg.	digitalis	quinidine	normal rhythm	
slight	none	hypertension, slight enlargement	digitalis (overdigitalized)	stopped digitalis	normal rhythm	changed to aur. flbr. and then to normal rhythm
marked	present	hypertension, enlargement		digitalis	normal rhythm	developed acute edema of lungs
incidental	none	arteriosclerosis	digitalis			changed to auricular fibrillation
none	none	arteriosclerosis			normal rhythm	
none	none	exophthalmic goitre			normal rhythm	
slight	none	arteriosclerosis, slight enlargement	quinidine	digitalis	normal rhythm	A-V block very brief
marked	present	hypertension, enlargement		digitalis	normal rhythm	
incidental	acute edema of lungs	acute myocardial infarction, hypertension, enlargement	digitalis		normal rhythm	P waves vary in form
incidental	present	old myocardial infarction	digitalis		normal rhythm	

PREVIOUSLY REPORTED CASES

The first report of auricular paroxysmal tachycardia with partial A-V block was by Koplik,[2] in 1917. The patient was a 10-year-old boy. Many electrocardiograms were obtained, but none were published. In 1922, Singer and Winterberg[3] published curves from a 70-year-old man whose A-V block was complete, with a ventricular rate of 26 per minute. The auricular paroxysmal tachycardia was stopped by quinine given intravenously. Gallavardin,[4] in 1923, described a case in which there were frequent dropped ventricular beats and short periods of 2:1 A-V

block interspersed with short runs of 1:1 response. He pointed out that such a disturbance could give rise to almost complete irregularity of the ventricles at a rapid rate, closely resembling auricular fibrillation clinically. In 1924, Lenhartz and Samet[5] reported a case in a 29-year-old nurse who for a long time was thought to have auricular fibrillation. Normal rhythm was finally restored by the combined use of physostigmine and digitalis after the attack had lasted ninety-four days. Sprague and White,[6] in 1925, reported three cases, and briefly compared and contrasted them with auricular flutter. They pointed out that the attacks occurred over a period of years, often lasted several days, and were not influenced favorably by quinidine, but could often be stopped by digitalis in full doses. In 1927, Wenckebach and Winterberg[7] reported three cases, in two of which normal rhythm was restored by quinine. Dock,[8] in 1928, described a case in which the auricular paroxysmal tachycardia lasted for twenty-two days and was accompanied by partial A-V block varying in degree from 2:1 to 4:1, and was not affected appreciably by pressure upon the carotid sinus or the eyes or by large amounts of digitalis. In 1934, Mackinnon[9] reported two cases. One of these was clearly an instance of auricular paroxysmal tachycardia with partial A-V block. The other was similar in most important respects, but can be considered only as a probable case because the auricular waves could not be identified in the records. The author pointed out that in occasional cases of auricular paroxysmal tachycardia the ventricular rhythm may be irregular, and that the usual cause for this irregularity is defective conduction in the A-V bundle.

Brown,[10] in 1936, presented esophageal leads of two patients, which he interpreted as showing auricular paroxysmal tachycardia with partial A-V block. The first of these curves is susceptible of an alternative interpretation, namely, that, while the rate was rapid, the ventricular complexes were slightly aberrant and thus gave the curve an appearance which somewhat resembled auricular paroxysmal tachycardia with partial A-V block. The second case, however, is clearly a very interesting example of the condition under discussion, and illustrates the value of digitalis in its treatment. The author called attention to the differences between auricular paroxysmal tachycardia and auricular flutter as shown by esophageal leads. In the former the auricular deflections are separated one from another by intervals during which the tracing remains at the isoelectric level. In flutter, however, the auricular activity produces a continuous oscillation of the tracing, with no isoelectric intervals, suggesting continuous excitation.

In 1937, Maddox[11] reported a case of auricular paroxysmal tachycardia with variable A-V conduction and periods of 2:1 or 3:1 block. His discussion deals mainly with the site of impulse formation and the influence of the extrinsic cardiac nerves. Maarssø,[12] in 1937, reported a case in which an attack of auricular paroxysmal tachycardia lasted longer than one month. At times there was partial A-V block, varying

in degree from frequent dropped beats to 2:1 response. Fine and Miller,[13] in 1940, reported a remarkable case of orthostatic auricular paroxysmal tachycardia in which the rate was influenced by posture. Sometimes the paroxysmal tachycardia was present while the patient was recumbent, and was then sometimes accompanied by partial A-V block with frequent dropped beats. The attacks of paroxysmal tachycardia could be prevented by either digitalis or quinidine.

Lewis[1] published electrocardiograms of a child with auricular paroxysmal tachycardia and partial A-V block with occasional dropped beats. The auricular rate was 290 per minute, and the P waves were upright in Lead II. Recently, Katz[14] has published the curves of three patients who had partial A-V block during paroxysms of auricular tachycardia. The first of these showed auricular rates of 180 to 125 and block varying in degree from dropped beats to 2:1. The second had an auricular rate of 158 and 2:1 block. The third patient had an auricular rate of 167 and frequent dropped beats. In all three cases the P waves were upright during the paroxysms. These cases are not included in the table because the clinical data were not given.

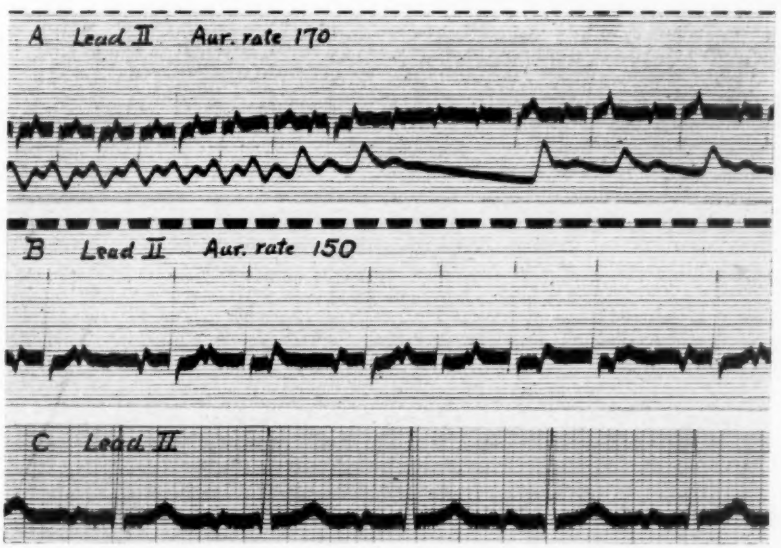

Fig. 1.—Case 1. *A*, March 22, 1922. Lead II and radial pulse. Auricular rate, 170. *B*, Aug. 2, 1922. Lead II. Auricular rate 150. *C*, July 26, 1924. Lead II. Normal rhythm, rate 90.

CASE REPORTS

CASE 1.*—A white man, aged 39 years, was first seen in 1922. He complained of attacks of palpitation and dyspnea brought on by exertion. These began in 1913, and had been worse since 1917. Examination revealed no evidence of organic heart disease and no signs of congestive cardiac failure. The electrocardiogram (Fig. 1, *A* and *B*) showed diphasic P waves, occurring at a rate of 170 per minute.

*This case is included through the kindness of Dr. John Parkinson, London, England, who generously furnished the electrocardiograms and the clinical data.

Partial A-V block of varying degree (1:1, 3:2, 2:1) was present. Full doses of quinidine sulfate had no effect on the auricular deflections. The average ventricular rate was somewhat increased and the ventricular complexes became aberrant. One week later digitalis was given in full doses. This increased the degree of A-V block (frequently 3:1), but had no further effect. In 1924, an electrocardiogram showed normal rhythm with diphasic P waves and a rate of 90 (Fig. 1, *C*). In 1927, the patient stated that he had been fairly well, and tracings again showed normal rhythm with diphasic P waves and a rate of 100.

CASE 2.—A white man, 32 years of age, was first seen Oct. 28, 1937. At the age of 12 years he had rheumatic fever. He had a brief attack of tachycardia in 1928, and another in 1929. After that he had frequent attacks of tachycardia, brought on by slight exertion, by eating large meals, or by constipation, and sometimes relieved by rest. The paroxysms sometimes lasted for several hours or days, and were then accompanied by shortness of breath and soreness in the region of the liver. They became so frequent, so prolonged, so severe, and so resistant to treatment that recourse was had to morphine, with resulting addiction.

When first seen, the patient was exhausted from a prolonged attack of tachycardia. The heart rate was 200, the rhythm regular. Pressure upon the carotid sinus caused no change. Mecholyl, in a dose of 25 mg., was given subcutaneously, and repeated fifteen minutes later. After this the heart rate became a little slower, and upon carotid sinus pressure it fell to a normal level. Almost immediately, however, the rapid beating returned.

At this point the first electrocardiogram was taken; it showed auricular flutter with an auricular rate of 286, and 2:1 ventricular response. Digitalis, in a dose of 0.5 Gm., was given intravenously, and thirty minutes later the electrocardiogram (Fig. 2, *A*) showed auricular flutter with an auricular rate of 275 and a ventricular rate of 82 per minute. On October 29, digitalis, in a dose of 0.35 Gm., was given intravenously. On November 1 the electrocardiogram (Fig. 2, *B*) showed auricular paroxysmal tachycardia with auricular and ventricular rates of 200. Digitalis (0.35 Gm.) was given intravenously, and fifteen minutes later there was 2:1 A-V block; the auricular rate was still 200 (Fig. 2, *C*). After this, digitalis was given orally in rather large amounts. The auricular paroxysmal tachycardia continued, but partial A-V block was maintained, and on November 22 the electrocardiogram (Fig. 2, *D*) showed an auricular rate of 200 and a ventricular rate of 64, sometimes even lower. Precordial leads were used in order to obtain large auricular deflections. At this time digitalis was stopped because of symptoms of mild intoxication. On November 26 there was 1:1 ventricular response with a rate of 200. Carotid sinus pressure caused partial block. After giving mecholyl (25 mg. subcutaneously), carotid sinus pressure caused pronounced slowing of the ventricles. Esophageal leads were used to record this (Fig. 2, *E*), and showed large auricular deflections separated by periods of electrical quiescence. Digitalis was resumed. On Dec. 29, 1937, normal rhythm was present (Fig. 2, *F*). For several months after this there were many attacks of tachycardia. The patient then improved and it was thought that normal rhythm was present much of the time. At this time the murmur of mitral stenosis was heard. On Oct. 28, 1938, however, an electrocardiogram showed auricular flutter in Leads I and II, with an auricular rate of 292 and a 4:1 ventricular response. A minute later, when Lead III was taken, auricular fibrillation was present, with a ventricular rate of 80. In order to bring out the auricular waves more clearly, a precordial lead was used (Fig. 2, *G*).

CASE 3.—A white man, aged 41 years, was first seen on Jan. 5, 1938. For one month he had been having attacks of tachycardia, shortness of breath, and dizziness. They occurred irregularly every few days and lasted a few minutes. They were abrupt in onset and termination, and were brought on by exertion and relieved by

rest. Similar attacks had occurred one year previously and again six months previously, each time for a period of a few weeks.

Physical examination was entirely negative. No abnormality of the heart was detected. The blood pressure was 118/60. The rhythm was regular, the rate, 100. With moderate exercise, however, the rate rose to more than 160; the rhythm was regular. After about thirty seconds the rate dropped abruptly and the rhythm was

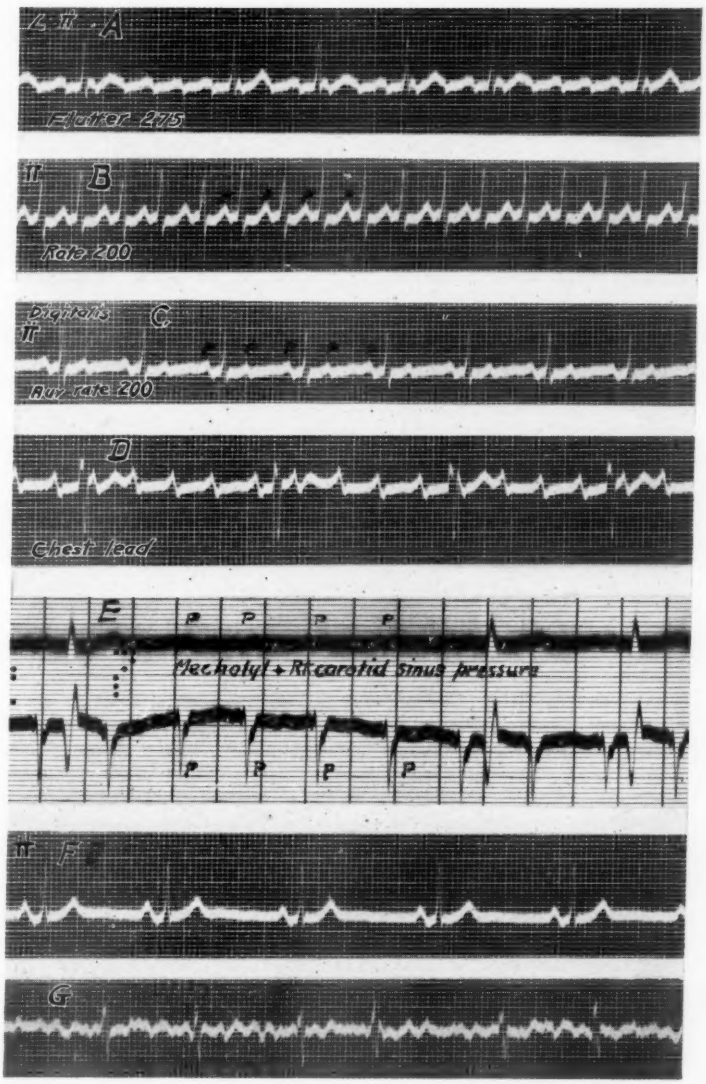

Fig. 2.—Case 2. *A*, Oct. 28, 1937. Lead II. Auricular flutter. Auricular rate 275, ventricular rate, 82. *B*, Nov. 1, 1937. Lead II. Auricular paroxysmal tachycardia with auricular and ventricular rates of 200. Patient had had digitalis (0.85 Gr.). *C*, Nov. 1, 1937. Lead II, 15 minutes after 0.35 Gm. of digitalis intravenously. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate 200. *D*, Nov. 22, 1937. Precordial lead. Auricular paroxysmal tachycardia with high grade partial A-V block. Auricular rate 200. Patient had had large amounts of digitalis. *E*, Nov. 26, 1937. Lead I and esophageal lead. Pressure upon right carotid sinus after 25 mg. of mecholyl subcutaneously. *F*, Dec. 29, 1937. Lead II. Normal rhythm. *G*, Oct. 1, 1938. Precordial lead. Auricular fibrillation.

irregular for 10 or 15 beats. Thereafter the heart beat regularly at a normal rate. The exercise was repeated and the same changes in rate and rhythm were again observed.

An electrocardiogram (Fig. 3, *A*) showed paroxysmal tachycardia with an auricular rate of 200 and partial A-V block, usually 3:1. A precordial lead (Fig. 3, *B*) was employed to show the auricular waves more clearly. Exercise permitted the ventricles to follow the auricles at their full rate for a short time, after which the partial block returned. Carotid sinus pressure and mecholyl failed to terminate the auricular tachycardia. Quinidine sulphate, in a dose of 0.4 Gm. orally, was followed in two hours by slowing of the auricles to 174; the ventricles followed at

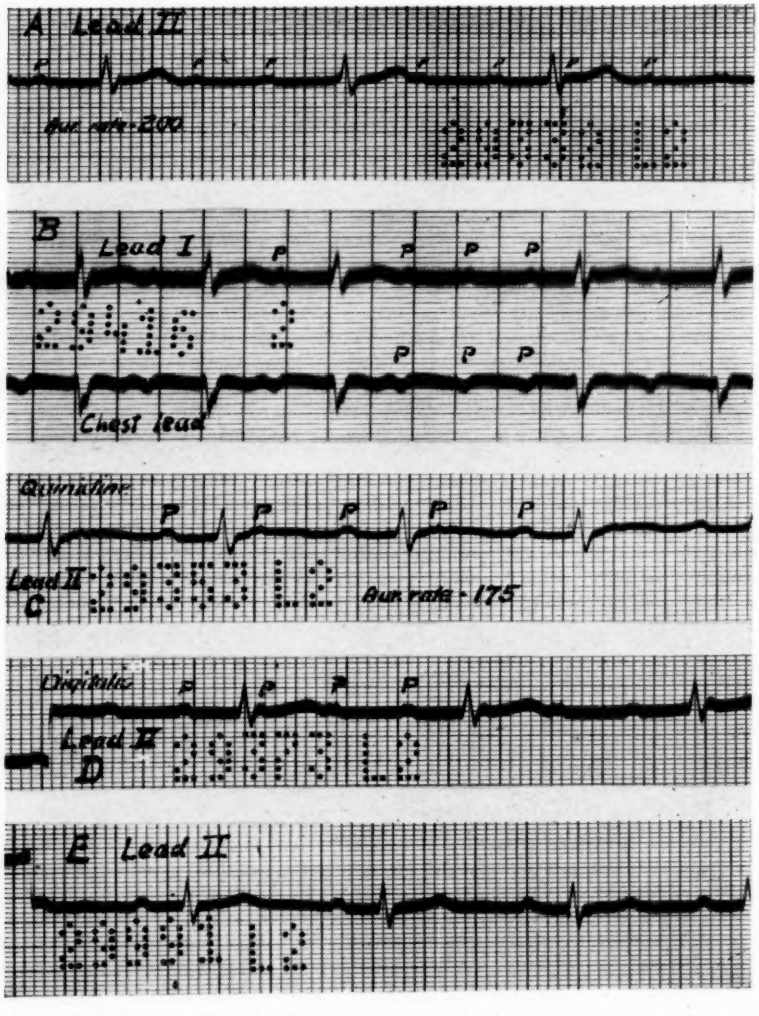

Fig. 3.—Case 3. *A*, Jan. 5, 1938. Lead II. Auricular paroxysmal tachycardia with partial A-V block. Auricular rate 200. Ventricular 78. *B*, Jan. 5, 1938. Lead I above and precordial lead below. Pressure upon right carotid sinus. Auricular rate 200. *C*, Jan. 7, 1938. Lead II, 2 hours after 0.4 Gm. of quinidine sulfate. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate, 175. Ventricular rate, 87. *D*, Jan. 10, 1938. Lead II, after 1.3 Gm. of digitalis. Auricular paroxysmal tachycardia with 3:1 A-V block. Auricular rate, 202. Ventricular rate, 67. *E*, March 17, 1938. Lead II. Normal rhythm, rate 88. Had taken digitalis regularly.

half the auricular rate (Fig. 3, *C*). Normal rhythm, however, was not restored. The patient was then digitalized without affecting the auricular rate. The degree of block, however, was increased, usually to 3:1 (Fig. 3, *D*), and the rapid ventricular beating upon exertion was prevented. After digitalization it was observed that mecholyl, in a dose of 15 mg. subcutaneously, increased the auricular rate from 207 to 218; the ventricular rate rose to 109.

Digitalis was continued. The patient returned January 26, at which time he had complete relief from his symptoms. The auricular rate was 211, and the ventricular rate, 86, with a mixture of 2:1 and 3:1 block. On March 17 the patient stated that he had been entirely free of symptoms, and the electrocardiogram showed normal rhythm (Fig. 3, *E*).

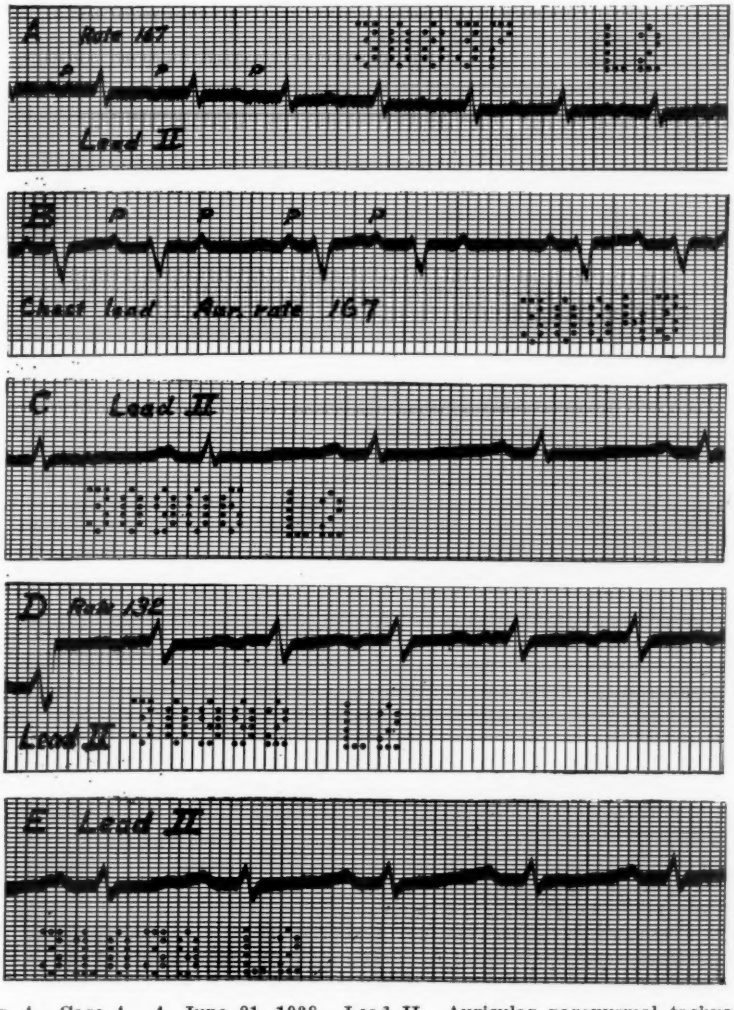

Fig. 4.—Case 4. *A*, June 21, 1938. Lead II. Auricular paroxysmal tachycardia, rate 167. Patient had received quinidine and digitalis. *B*, June 21, 1938. Precordial lead, with carotid sinus pressure. There is partial A-V block with dropped beats. The auricular deflections are shown more clearly. Auricular rate 167. *C*, June 29, 1938. Lead II. Normal rhythm. Rate 97. Had had digitalis and quinidine. *D*, July 11, 1938. Lead II. Auricular paroxysmal tachycardia with 1:1 ventricular response. Rate 132. Had had digitalis and quinidine. *E*, July 18, 1938. Lead II. Normal rhythm. Rate 107.

CASE 4.—A white boy, 15 years of age, was admitted to the hospital June 21, 1938. He had been in excellent health until May 1, 1938 when he began having shortness of breath upon moderate exertion, tachycardia, weakness, and an unproductive cough. The patient was not aware of an abrupt onset, nor was there any known infection at the time. The tachycardia persisted around 200 per minute in spite of rest in bed. The shortness of breath was increased by lying flat. Digitalis slowed the ventricles by producing partial A-V block. Quinidine slowed the auricular rate but was otherwise without appreciable effect. The patient grew weaker and more dyspneic, and the liver became enlarged. He was then referred to the hospital.

Upon physical examination the patient appeared seriously ill, with a dusky cyanosis, and dyspnea upon lying flat. The heart was moderately enlarged. There was a systolic murmur over the entire heart, loudest at the apex. No diastolic murmur was heard. The rate was about 160; the rhythm was not remarkable apart from an occasional, slight irregularity. The blood pressure was 92/70. The lungs were normal. The liver was slightly enlarged. There was no edema.

Roentgenologic examination showed fairly marked cardiac enlargement.

The electrocardiogram showed a heart rate of 167; the rhythm was regular except for occasional dropped beats (Fig. 4, *A*). Precordial leads showed the auricular deflections more clearly. Pressure upon the carotid sinus increased the degree of A-V block, causing frequent dropped beats (Fig. 4, *B*). Quinidine was withheld, and the auricular rate rose to 176; then quinidine was resumed and the auricular rate fell to 150. After the administration of both digitalis and quinidine for several days, normal rhythm returned (Fig. 4, *C*). In a few days, however, the tachycardia returned and persisted, except for a brief period of normal rhythm on July 18 (Fig. 4, *E*). During the ectopic auricular tachycardia, the rate slowed to 132 under digitalis and quinidine (Fig. 4, *D*). The patient grew progressively worse; he showed no improvement during the interludes of normal rhythm or when the rate slowed to 132. Râles appeared in the lungs and edema of the legs developed. The patient died July 24, 1938, of cardiac failure.

At autopsy the heart weighed 350 grams. It showed myocardial hypertrophy microscopically. There were marked subendocardial vacuolar degeneration and moderate subepicardial fatty infiltration. Infarction of the left ventricle in the region of the conduction apparatus was found. There was also a degenerative subendocardial lesion in the left ventricle, with necrosis, lymphocytic infiltration, and fibroblastic proliferation. An organizing mural thrombus was present in the left ventricle. There was endocardial sclerosis.

The lungs showed an acute exacerbation of chronic passive congestion, with edema. There were multiple fresh, and older, hemorrhagic infarctions. There were organizing thrombi in the pulmonary veins. The smaller arteries were sclerotic. There was an embolus in a medium-sized pulmonary artery, and a bland embolus in the main pulmonary artery. Acute purulent bronchitis and terminal purulent lobular pneumonia were present.

The liver and spleen showed chronic passive congestion.

CASE 5.—A white woman, aged 62 years, entered the hospital July 11, 1938. During the previous ten months she had had recurring attacks of left-sided renal colic, suffered from increasing weakness, and had lost 35 pounds in weight. During this time she was short of breath upon moderate exertion, and experienced frequent palpitation and irregularity of the heart. There was occasional swelling of the ankles.

Physical examination showed that the heart was normal in size. There was a systolic murmur at the apex. The rate varied from 106 to 140. There was an irregularity which was attributed to dropped beats. The blood pressure was 130/85. The radial and brachial arteries were thickened. The lungs were normal. The

abdomen was negative. There was no edema. The isthmus of the thyroid contained a small adenoma.

Roentgenologic examination showed no abnormalities of the heart or lungs, but did reveal a renal calculus on the left side.

The electrocardiogram showed an auricular rate of 167. Partial A-V block, with frequent dropped beats, was present, and the ventricular rate was 134 (Fig. 5, *A*). Carotid sinus pressure increased the degree of block and slowed the ventricles, but did not alter the auricular mechanism (Fig. 5, *B*). After digitalis in full doses, normal rhythm returned (Fig. 5, *C*). The patient was sent back to her home physician for nephrectomy.

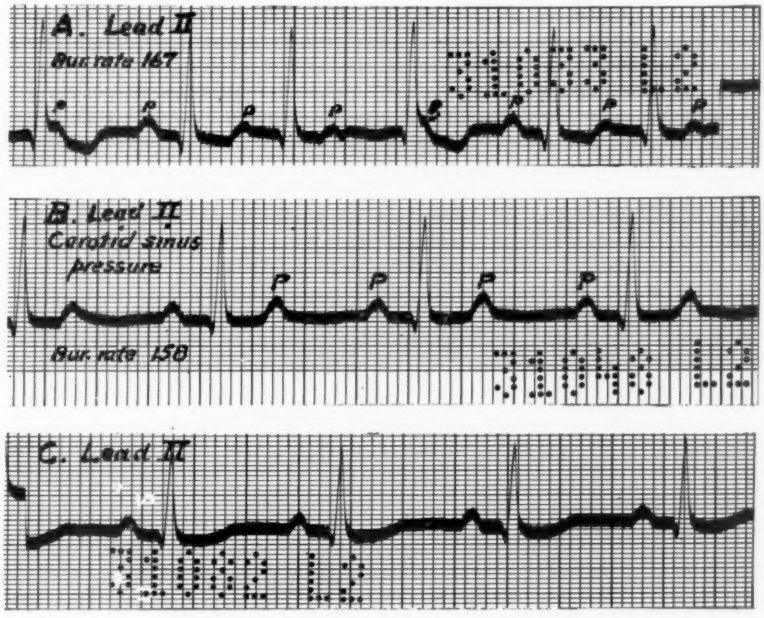

Fig. 5.—Case 5. *A*, July 18, 1938. Lead II. Auricular paroxysmal tachycardia with partial A-V block and frequent dropped ventricular beats. Auricular rate 167. *B*, July 19, 1938. Lead II. Carotid sinus pressure produces 2:1 A-V block. Auricular rate 158. *C*, July 22, 1938. Lead II. Normal rhythm. Rate 93. Had had digitalis.

CASE 6.—A white man, 19 years of age, was admitted to the hospital July 18, 1938. In 1930, the patient had had epigastric pain, nausea, and vomiting; these were attributed by his physician to heart disease, and were relieved in a few days by rest and digitalis. After that he took digitalis almost continuously and restricted his activities. Similar symptoms returned in 1933, and again in January, 1938. In each instance they followed strenuous exertion and were relieved by rest in bed. In January, 1938, he had a brief, acute respiratory infection. After that he had dyspnea and pronounced tachycardia upon moderate exertion. The heart was slow during rest. He improved under larger doses of digitalis and a month of rest in bed. The tachycardia upon exertion persisted, however, and he was referred to the hospital. There was no history of rheumatic fever.

The physical examination was entirely negative with the exception of the heart. It was markedly enlarged, with dullness extending to the left anterior axillary line. There were systolic murmurs at the apex and base. The rate and rhythm varied. At times the heart was regular at a rate of 60, at other times regular at a rate

of 170. Occasionally the rhythm was irregular and the rate intermediate between the two extremes. The blood pressure varied within normal limits. There were no signs of congestive cardiac failure.

Roentgenologic examination showed marked cardiac enlargement.

The electrocardiograms showed tachycardia of auricular origin, with a rate of 162 and 2:1 A-V block (Fig. 6, *A*). After mild exercise there was transient 1:1 ventricular response with no change in auricular rate. Carotid sinus pressure in-

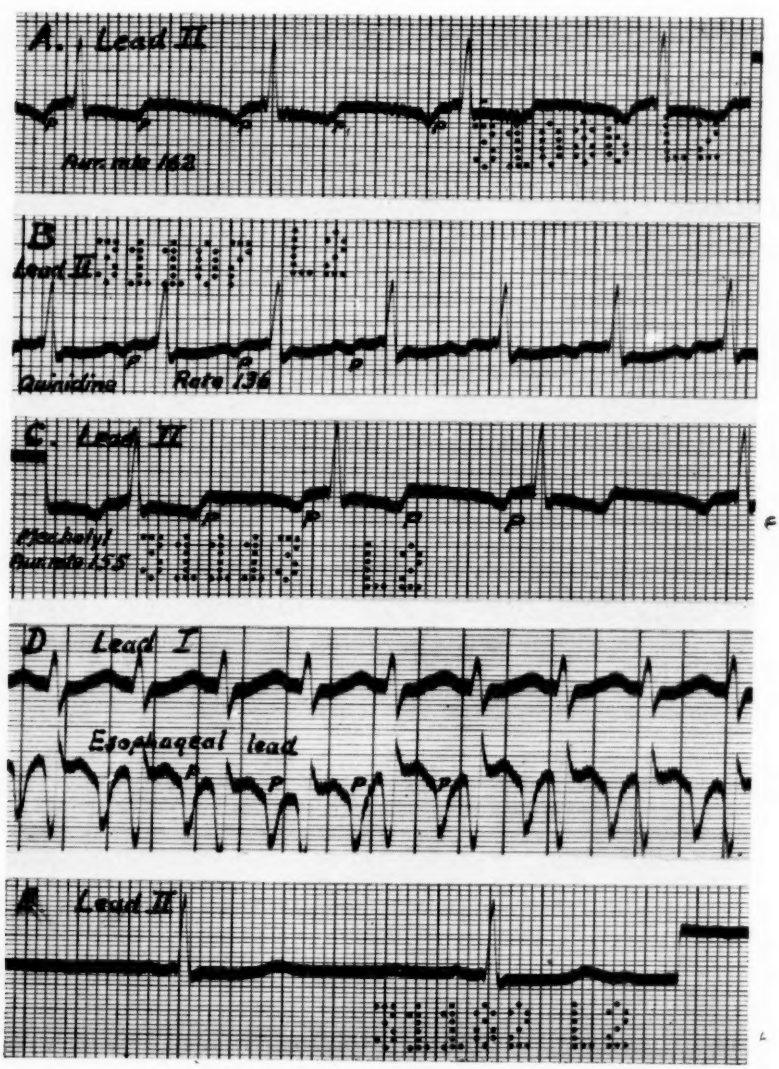

Fig. 6.—Case 6. *A*, July 22, 1938. Lead II. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate 162. Had had digitalis. *B*, July 25, 1938. Lead II. Auricular paroxysmal tachycardia with 1:1 ventricular response. Rate 136. Had had digitalis and quinidine. *C*, July 26, 1938. Lead II, taken 33 minutes after 10 mg. of mecholyl subcutaneously. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate 155. *D*, Aug. 8, 1938. Lead I above, esophageal lead below. Auricular paroxysmal tachycardia with 1:1 ventricular response. Rate 155. The auricular waves are very large in the esophageal lead. *E*, Aug. 3, 1938. Lead II. Normal rhythm. Rate 50. Had had digitalis and quinidine. Intraventricular block is present, but not readily apparent in this lead.

creased the degree of block temporarily, but did not affect the auricular mechanism or rate. Quinidine slowed the auricles to 136, usually with 2:1 ventricular response, but sometimes with 1:1 response (Fig. 6, *B*). Mecholyl, in a dose of 10 mg. subcutaneously, increased the degree of block slightly, but did not alter the auricular rate (Fig. 6, *C*). Normal rhythm returned on July 31, after large doses of quinidine sulfate (Fig. 6, *E*). On August 7 auricular paroxysmal tachycardia returned (Fig. 6, *D*). Normal rhythm was resumed after 0.9 Gm. of quinidine on August 8, and persisted thereafter. The patient was given quinidine sulfate in a dose of 0.3 Gm. three times daily. He felt quite well and there was no evidence of quinidine intoxication. He died unexpectedly in his sleep on Aug. 13, 1938.

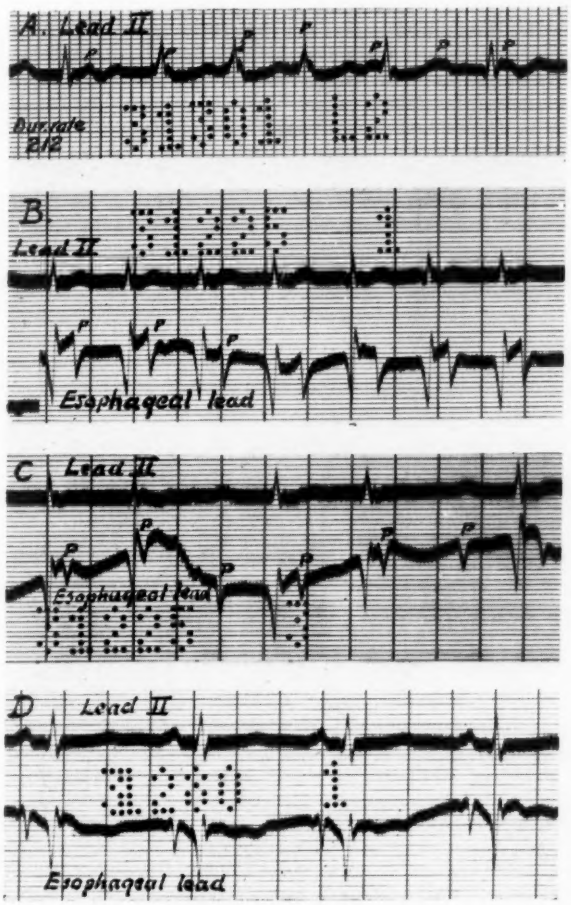

Fig. 7.—Case 7. *A*, Aug. 17, 1938. Lead II. Auricular paroxysmal tachycardia with partial A-V block and many dropped ventricular beats. Auricular rate, 212. Had had digitalis and quinidine. *B*, Aug. 6, 1938. Lead II above, esophageal lead below. There is 1:1 ventricular response. *C*, Same as *B*, but showing partial A-V block. *D*, Aug. 13, 1938. Lead II above, esophageal lead below. Normal rhythm. The auricular deflections are very large in the esophageal leads.

Autopsy showed hypertrophy of the left ventricle, the lateral wall of which measured 28 mm. in thickness. There was an old mitral valvulitis, with minimal deformity of the valve. The right side of the heart was dilated. The lungs showed congestion and edema, patchy emphysema, and atelectasis. There were acute puru-

lent bronchitis and microscopic bronchiectasis. The persistent hyperplastic thymus, generalized lymphoid hyperplasia, and hypoplasia of the aorta and adrenals suggested thymicolymphatic constitution. There was slight chronic cholecystitis, and the liver contained foci of leucocytes. The brain was not examined.

CASE 7.—A white man, aged 67 years, entered the hospital Aug. 1, 1938. He had been in good health until seven years previously, when he had a sudden attack of dyspnea which was relieved by adrenalin. Thereafter he had dyspnea when excited, and then upon moderate exertion; this increased in severity until finally he was short of breath at rest, and for the preceding few weeks he had been orthopneic. He spent the ten days before admission in a chair because of dyspnea, swelling of the legs, and sleeplessness. In four years he lost 65 pounds. There was no cough, wheezing, or chest pain.

Physical examination showed that the chest was emphysematous, with hyperresonance more pronounced on the right side. The breath sounds were absent over the right side of the chest, except in the interscapular region, where they seemed normal. There were râles at the base of the left lung. The heart was not definitely enlarged; the rate and rhythm were normal. There were no murmurs. The blood pressure was 180/106. The peripheral arteries were sclerotic. There was marked edema of the ankles.

Roentgenologic examination showed emphysema of the lungs, pneumothorax on the right, an old fibrotic scar at the left apex, and probably an inflammatory lesion at the right base. There was no abnormality of the heart or aorta.

The electrocardiogram on August 1 showed occasional auricular extrasystoles, but was normal in other respects. Digitalis was given in full doses. The patient had several attacks of auricular paroxysmal tachycardia, with partial A-V block (Fig. 7). Esophageal leads were employed to show the auricular deflections more clearly. The tachycardia was controlled only by fairly large doses of quinidine. The pneumothorax and edema cleared up satisfactorily, and the paroxysmal tachycardia did not return. The dyspnea upon slight exertion persisted. Upon one occasion tracings showed what was probably A-V nodal rhythm, with a rate of 88 per minute; the rhythm was regular, but no auricular waves could be identified.

CASE 8.—A white man, 53 years of age, entered the hospital Aug. 25, 1939. For the preceding eighteen months he had suffered from fatigue, shortness of breath, and swelling of the legs. For many years he had had a cough productive of yellowish sputum.

Physical examination showed emaciation, dyspnea, cyanosis, and pronounced edema of the feet, legs, and thighs. The lungs were resonant, but contained numerous crepitant and coarse râles throughout, and there were small areas of bronchovesicular breath sounds over the upper lobes. The heart was considerably enlarged, and there was a loud systolic murmur over the lower end of the sternum. The rhythm was regular except for occasional extrasystoles. The blood pressure was 110/78. The peripheral arteries were thickened. The liver was slightly enlarged.

Roentgenologic examination showed marked enlargement of the heart. In the lungs there were increased vascular shadows and also areas of inflammatory infiltration.

The electrocardiogram on August 26 showed normal rhythm, with occasional ventricular extrasystoles. There was right axis deviation, with inverted T waves in Leads II and III (Fig. 8, *A*). The patient was given digitalis in moderate amounts and improved temporarily, but there was no striking change at any time. On August 30 the electrocardiogram (Fig. 8, *B*) showed auricular paroxysmal tachycardia with an auricular rate of 188, and partial A-V block with a ventricular rate of 112. Later the rhythm became regular at a slower rate, and the curve of Sep-

tember 1 showed what was probably A-V nodal rhythm (Fig. 8, *C*), without any deflections which could be identified as P waves. The patient then grew gradually worse and died Sept. 5, 1939.

Autopsy showed bilateral saccular and tubular bronchiectasis and bronchiectatic abscesses. There were mucopurulent bronchitis and an old fibrous tuberculosis of the lungs and bronchial lymph nodes. The heart weighed 400 grams and showed right-sided dilatation. There were myocardial hypertrophy and brown atrophy. There were extensive subendocardial fibrosis and subepicardial fatty infiltration. There was minimal sclerosis of the coronary arteries and of the mitral and tricuspid valve leaflets.

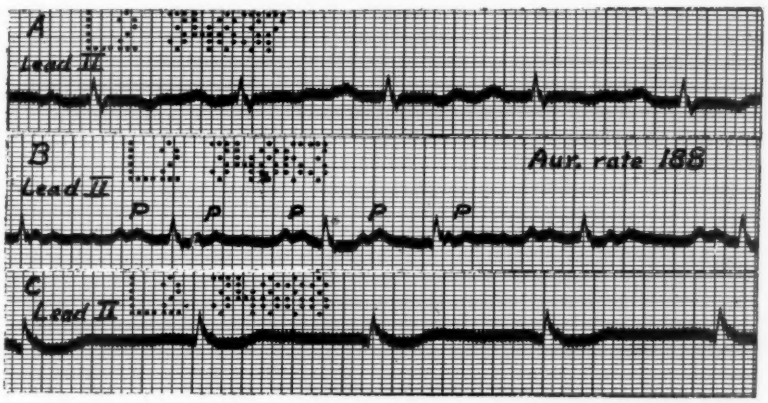

Fig. 8.—Case 8. *A*, Aug. 26, 1939. Lead II. Normal rhythm. Rate 107. *B*, Aug. 30, 1939. Lead II. Auricular paroxysmal tachycardia with partial A-V block, usually 2:1. Auricular rate 188. Had had digitalis. *C*, Sept. 1, 1939. Lead II. Probably A-V nodal rhythm. Rate 88. No auricular deflections visible.

Case 9.—A white woman, 23 years of age, was followed closely throughout the winter of 1939-1940, during a pregnancy. She gave a history of rheumatic fever in childhood, but tolerated exertion fairly well. Examination showed very slight cardiac enlargement, a blowing systolic murmur at the base, a high-pitched diastolic murmur at the left sternal margin, and a low-pitched diastolic murmur at the apex. The rate and rhythm were normal. The blood pressure was usually about 100/60. There were no signs of congestive failure.

The patient did well until March 7, 1940, when she developed acute edema of the lungs, from which she made a good recovery. On April 30, 1940, when almost at term, she was delivered of a normal infant by low Caesarean section, from which she recovered satisfactorily. Digitalis was continued in a dose of 0.1 Gm. daily. The cardiac rhythm remained normal throughout.

On July 18, 1940, she had a short attack of palpitation. On July 20 she developed shortness of breath and rapid, violent beating of the heart upon very slight exertion. Physical examination showed nothing new except slight cardiac irregularity and rather pronounced pulsation of the neck veins. The cardiac rate was 100. Upon rather mild exertion the rate rose to 210 and the rhythm was regular. The rate gradually fell to the previous level and slight irregularity returned. Pronounced but transient slowing was produced by carotid sinus pressure.

The electrocardiograms, which had previously shown normal rhythm, with broad, notched P waves (Fig. 9, *A*), now showed auricular paroxysmal tachycardia with an auricular rate of 195 (Fig. 9, *B*). There was high-grade partial A-V block, with a ventricular rate of 100. After exercise the auricular rate was 219. The

ventricles responded to each auricular beat for a short time (Fig. 9, *C*), then became slower and irregular, and finally displayed a long period of near standstill, interrupted by idioventricular beats (Fig. 9, *D* and *E*), at the end of which they resumed their previous rate of 100 per minute.

The dose of digitalis was increased for a few days, but the shortness of breath and palpitation continued, although they were less easily brought on. Quinidine was given and the patient tolerated moderate exertion without symptoms. The quinidine was stopped for a few days and the palpitation and shortness of breath returned. When quinidine was resumed the symptoms ceased. Since then quinidine has been taken irregularly. Tachycardia occurs every few days, often when quinidine has not been taken. Small amounts of quinidine are followed by normal rhythm in one or two hours.

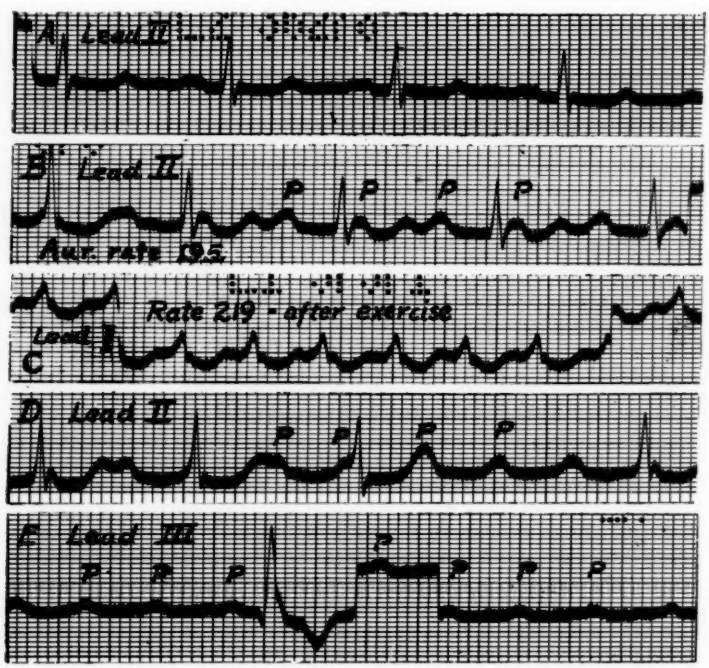

Fig. 9.—Case 9. *A*, March 12, 1940. Lead II. Normal rhythm, rate 90. *B*, July 20, 1940. Lead II. Auricular paroxysmal tachycardia, with partial A-V block. Auricular rate 195. Ventricular rate 100. Patient had had digitalis. *C*, *D*, and *E*, Leads I, II, and III, resp., July 20, 1940. After exercise, 1:1 ventricular response is followed by slowing and irregularity of the ventricles, with a period of ventricular near-standstill interrupted by idioventricular beats.

Case 10.—A white man, aged 54 years, was first seen Feb. 14, 1940. His blood pressure had been somewhat elevated for about six years, but there had been no symptoms associated with his hypertension except nocturia. The patient considered himself in good health until Feb. 12, 1940, when he had an attack characterized by a feeling of numbness in the precordium, nausea, and profound weakness. There was no pain or shortness of breath. Examination showed that the patient was overweight. There was slight enlargement of the heart, but no murmurs. The rate was about 70, and there were frequent premature beats. The blood pressure was 150/125. The remainder of the examination was negative. The electrocardiogram (Fig. 10, *A*) showed frequent auricular extrasystoles and slight left axis deviation, with inverted T waves in Lead I. The precordial leads were normal

with the exception of inversion of the T waves in the lead taken in the left anterior axillary line. There were no further attacks of this type. He was given theophylline and digitalis. After digitalization the dosage of this drug was reduced to 0.1 Gm. daily, but in September he took 0.2 Gm. daily.

During the night of Sept. 21, 1940, he began having vague precordial discomfort, described as a sense of pressure or numbness or shakiness, and nausea and vomiting. There was no pain, shortness of breath, or edema. He was given digitalis (0.4 Gm.) on September 23. Physical examination on September 24 showed that the heart was slightly enlarged. The rate varied between 44 and 52 per minute. There were periods of bigeminy. At times there were numerous premature beats. At other times the rhythm was regular. The heart sounds varied in intensity when the ventricles were beating slowly and regularly. Pulsations in the neck veins were counted at approximately 200 per minute. The blood pressure was 164/120. The

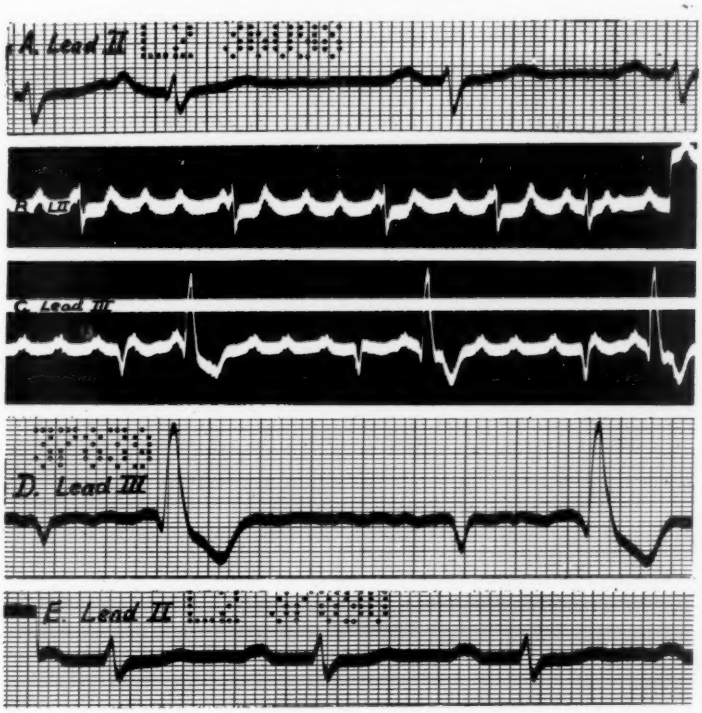

Fig. 10.—Case 10. *A*, Feb. 14, 1940. Lead II. Normal rhythm with auricular extrasystoles. P-R 0.20 sec. *B*, Sept. 24, 1940. Lead II. Auricular paroxysmal tachycardia with partial A-V block. Auricular rate 200. Ventricular rate 56. *C*, Sept. 24, 1940. Lead III. Auricular paroxysmal tachycardia with partial A-V block and extrasystolic bigeminy. Ventricular rate 58. In *B* and *C* the auricles are slightly irregular. Patient had been overdigitalized. *D*, Sept. 26, 1940. Lead III. Auricular fibrillation. Bigeminy. *E*, Oct. 2, 1940. Lead II. Normal rhythm. Prolonged P-R interval (0.28 sec.).

remainder of the examination was negative. The electrocardiograms showed auricular paroxysmal tachycardia with high-grade A-V block (Fig. 10, *B*). The auricular rate was 200, the ventricular rate, 56. There were ventricular extrasystoles and extrasystolic bigeminy (Fig. 10, *C*). Digitalis was stopped. Subsequent electrocardiograms showed auricular fibrillation (Fig. 10, *D*), and a few days later normal rhythm (Fig. 10, *E*). The patient dropped dead in December, 1941.

CASE 11.—A white man, 52 years of age, was admitted March 15, 1939, complaining of shortness of breath and swelling of the legs. These symptoms followed an acute respiratory infection which had occurred three weeks previously, and they became increasingly severe; the edema extended upward to include the abdomen. Examination showed that the heart was markedly enlarged; the rhythm was regular and the rate was 85. There were no murmurs. The blood pressure was 144/110. The arteries were not tortuous. There were dullness, diminished breath sounds, and râles at the bases of the lungs. The liver was enlarged and there was a little ascites. There was marked edema of the lower extremities, genitalia, and abdominal wall.

Roentgenologic examination showed marked enlargement of the heart.

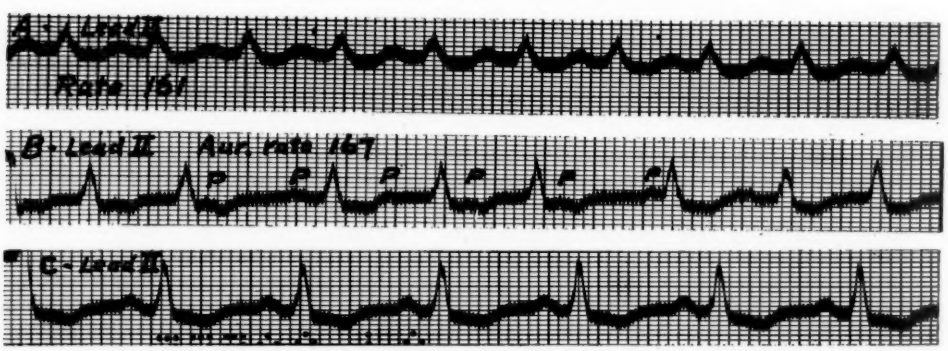

Fig. 11.—Case 11. *A*, March 18, 1939. Lead II. Paroxysmal tachycardia of supraventricular origin. Rate, 161. *B*, March 20, 1939. Lead II. After 2.4 grams of digitalis in 5 days. Auricular paroxysmal tachycardia with partial A-V block. Auricular rate 167, ventricular rate 131. *C*, March 21, 1939. Lead II. Normal rhythm, rate 107.

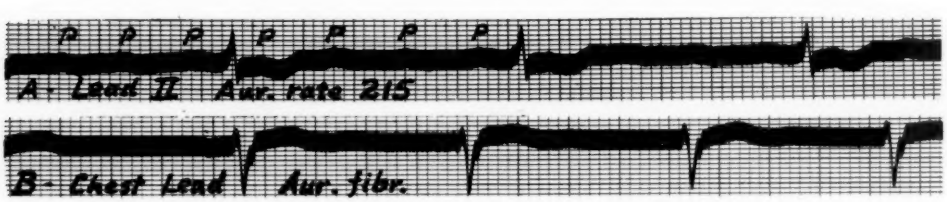

Fig. 12.—Case 12. *A*, Nov. 10, 1941. Lead II. Auricular paroxysmal tachycardia with 4:1 A-V block. Auricular rate, 215. *B*, Nov. 11, 1941. Precordial lead. Auricular fibrillation, ventricular rate 60.

On March 18 there occurred an attack of tachycardia which was shown by the electrocardiogram (Fig. 11, *A*) to be of supraventricular origin. The patient developed acute edema of the lungs, and the blood pressure rose to 170/120. He was almost moribund. By March 20 he had received 2.4 Gm. of digitalis in five days, and the tracing (Fig. 11, *B*) showed auricular paroxysmal tachycardia with partial A-V block. The auricular rate was 167, and the ventricular rate, 131, per minute. On the following day normal rhythm was present (Fig. 11, *C*). After this the patient improved remarkably; the blood pressure fell to 130/80 and the size of the heart returned almost to normal.

CASE 12.—A white man, aged 80 years, entered the hospital Nov. 8, 1941, because of urinary obstruction of three weeks' duration caused by benign enlargement of the prostate. He had suffered from shortness of breath for four years, and had been taking digitalis for three years. Examination showed evidence of senility

and emaciation. The heart was slightly enlarged and was irregular; the rate was 68. There were no murmurs. The blood pressure was 110/80. The peripheral arteries were thickened. The lungs were normal. The liver was not enlarged. There was edema of the left ankle which was attributed to varicose veins.

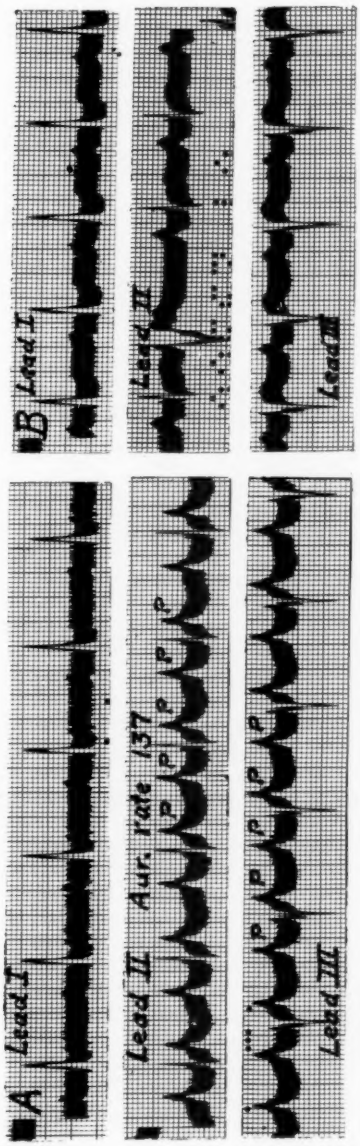

Fig. 13.—Case 13. *A*, May 25, 1935. Leads I, II, and III. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate 137. *B*, May 27, 1935. Leads I, II, and III. Normal rhythm with ventricular extrasystoles and prolonged P-R interval (0.24 sec.).

Digitalis, in a dose of 0.5 Gm., was given November 9. On the following day the electrocardiogram (Fig. 12, *A*) showed auricular paroxysmal tachycardia with partial A-V block, usually 4:1, with an auricular rate of 215 and a ventricular rate of 55 per minute. On November 11 the tracing (Fig. 12, *B*) showed auricular fibrillation with a ventricular rate of 60. There were many idioventricular beats, indicating overdigitalization. Subsequently the patient had a transurethral resection of the prostate, from which he made a good recovery.

CASE 13.—A white man, 68 years of age, was examined May 24, 1935. He had been troubled with attacks of nausea and vomiting. Examination showed that the heart was of normal size, but irregular, with a rate of 68 per minute. The lungs were normal, and the abdomen was negative. There was no edema. An electrocardiogram on the following day (Fig. 13, *A*) showed auricular paroxysmal tachycardia with 2:1 A-V block. The auricular rate was 137, and the ventricular rate, 68, per minute. There were a few ventricular extrasystoles. On May 27 the rhythm was normal except for ventricular extrasystoles (Fig. 13, *B*). A few months later the patient developed cardiac failure, but the cardiac rhythm remained normal.

CASE 14.—A white woman, 17 years of age, was admitted Nov. 1, 1932. She gave a history of nervousness, weakness, fatigue, palpitation, and irregularity of the heart. These symptoms began in August, 1931, and improved temporarily under iodine therapy in January, 1932. Enlargement of the thyroid gland appeared at that time. The palpitation was described as forceful beating of the heart, and the irregularity as a skipping of beats. No attacks or paroxysms of tachycardia or irregularity were noticed.

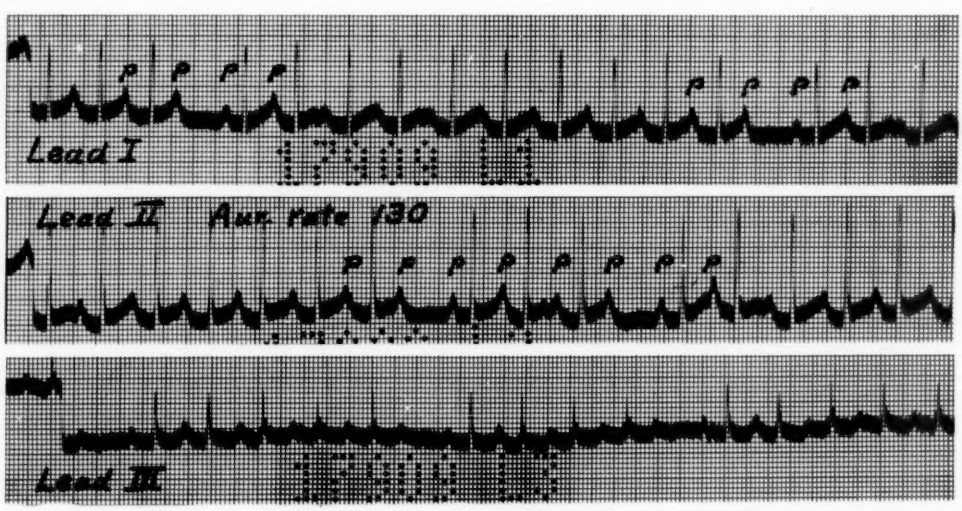

Fig. 14.—Case 14. Leads I, II, and III. Probably auricular paroxysmal tachycardia and partial A-V block with dropped beats. Auricular rate, 130.

Examination showed moderate enlargement of the thyroid, with a bruit over the gland. There were exophthalmos and a fine tremor of the fingers. The heart was normal in size, and there seemed to be numerous dropped beats. The rate was 108. There were no murmurs. The blood pressure was 135/78. There were no signs of congestive failure. The basal metabolic rate was plus 45 per cent. Roentgenologic examination showed no abnormality of the heart. The electrocardiogram (Fig. 14) showed an auricular rate of 130 and partial A-V block, with frequent dropped beats. Subsequently the rhythm seemed normal clinically, but no other electrocardiograms were taken. A subtotal thyroidectomy was followed by a good recovery. It is possible that this patient had auricular paroxysmal tachycardia with partial A-V block, but this is not certain.

CASE 15.—A white man, 64 years of age, was admitted Jan. 18, 1933. For four months he had suffered from attacks of rapid beating of the heart and shortness of breath; these lasted a few minutes and occurred several times a day. Exami-

nation showed that the patient was overweight. The heart was moderately enlarged, and there were faint systolic murmurs at the apex and base. The rhythm was irregular, and the rate was approximately 200 per minute. The blood pressure was 120, systolic. There were no signs of congestive cardiac failure. There were abrupt changes from tachycardia to normal rate, and from normal rate to tachycardia. The tachycardia was stopped by pressure upon the right carotid sinus, but soon returned. Many electrocardiograms were obtained, and showed a complicated arrhythmia. There were many brief attacks of tachycardia, apparently arising from two or more foci in the auricles, which had an abrupt onset and termination. There was also variation in the form of the ventricular deflections. In addition, there were brief periods of partial A-V block, as shown in Fig. 15. There were also premature ventricular deflections of abnormal outline, some of which probably were ventricular extrasystoles. Quinidine was given irregularly from January 21 to 24 without apparent benefit. Digitalization was begun on January 25 and completed on January 27, and then maintained by 0.1 Gm. daily. After this there were occasional auricular extrasystoles (Fig. 15, *D*), but no further attacks of tachycardia or dyspnea.

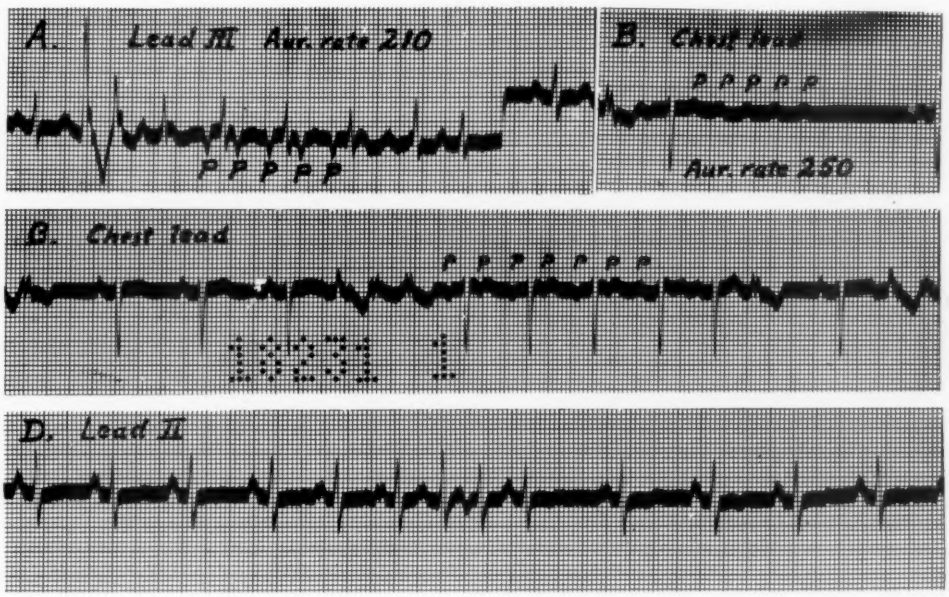

Fig. 15.—Case 15. *A*, Jan. 19, 1933. Lead III. A short paroxysm of tachycardia arising in at least two different foci in the auricles, and showing partial A-V block. Auricular rate 210. *B*, Jan. 21, 1933. Precordial lead. Unusual mode of termination of an attack; there is A-V block. Auricular rate 250. *C*, Jan. 21, 1933. Precordial lead. A short attack showing partial A-V block. Auricular rate approximately 200. *D*, Jan. 24, 1933. Lead II. Normal rhythm with auricular extrasystoles.

CASE 16.—A 26-year-old white woman entered the hospital March 13, 1929. For nearly a year she had suffered from shortness of breath, palpitation, swelling of the ankles, and nocturia. For the preceding month the swelling had been more extensive, involving the legs, thighs, and abdomen. There was no history of rheumatic fever.

Physical examination showed that the patient was dyspneic, orthopneic, and cyanotic. There was pronounced edema of both lower extremities, the right upper extremity, and the right breast. The heart was markedly enlarged. A systolic

murmur and gallop rhythm were present at the apex. No diastolic murmur was heard. The rhythm was regular, and the rate was 132 per minute. The blood pressure was 170/128. There were râles at the bases of the lungs. The liver and spleen were enlarged.

Roentgenologic examination showed marked cardiac enlargement and congestion of the lungs.

The electrocardiogram (Fig. 16, *A*) was taken March 16, 1929, after 1.8 Gm. of digitalis had been given. There was complete atrioventricular dissociation. The auricles and the ventricles were beating regularly and independently, the former at a rate of 160 and the latter at 84 per minute. No other electrocardiograms were obtained during this admission. The patient improved rapidly. Diuresis was accompanied by a loss of weight from 207 to 137 pounds. The blood pressure fell to 140/100, and the heart rate to 85.

The patient returned to the hospital July 31, 1931. Her symptoms and physical signs were essentially the same as on the previous admission. The blood pressure was 200/150. The heart rate varied from 90 to 75 per minute, and the electrocardiogram (Fig. 16, *B*) showed normal rhythm. In this curve the P waves are of different outline, as compared with the previous curve. The patient again improved.

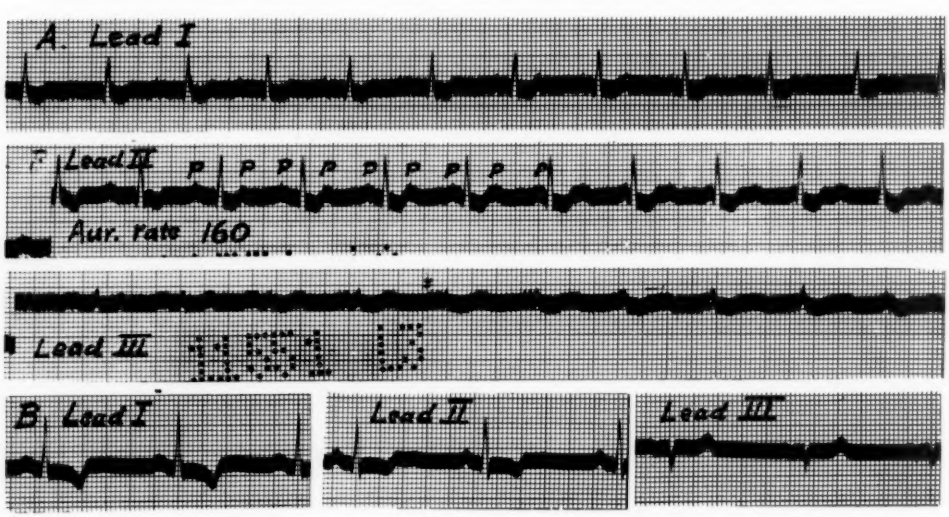

Fig. 16.—Case 16. *A*, March 16, 1929. Leads I, II, and III. Auricular paroxysmal tachycardia with complete dissociation. Auricular rate 160, ventricular rate, 84. *B*, Aug. 11, 1931. Leads I, II, and III. Normal rhythm.

CASE 17.—A 48-year-old white man entered the hospital May 12, 1942. He had felt well until one year previously. At that time he developed severe dyspnea during moderate exertion. It was relieved by morphine. His blood pressure was found to be 220. After that his pressure remained high, and he had headaches, blurred vision, and attacks of paroxysmal nocturnal dyspnea. Two months prior to admission his blood pressure was 240. A diagnosis of myocardial infarction was made by his physician. Since then he had been at rest in bed, and had taken digitalis regularly. There was no history of pain in the chest or edema of the extremities.

Physical examination showed an obese man who was dyspneic, orthopneic, and slightly cyanotic. The eye grounds showed evidence of retinal arteriosclerosis and

angiospasm. The heart was enlarged and was beating regularly at a rate of 120. The heart sounds were scarcely audible because of many coarse bubbling râles in the lungs. The blood pressure was 230/150. The peripheral vessels were not appreciably thickened. The liver was not enlarged. There was no edema of the extremities.

Shortly after admission, while being examined, the patient had an attack of acute pulmonary edema, from which he recovered after the administration of theophylline intravenously, and morphine, and phlebotomy, with the removal of 500 c.c. of blood, and the use of the oxygen tent. He was given 1.6 Gm. of digitalis in twelve hours, which caused nausea and vomiting. On the following day the patient was still somewhat dyspneic, and the blood pressure was 180/120. There was no pain in the chest. During the next few days the temperature rose to 99.6° F., the leucocyte count rose from 10,000 to 14,000 per c. mm., and the patient gradually improved. He was discharged May 26, 1942.

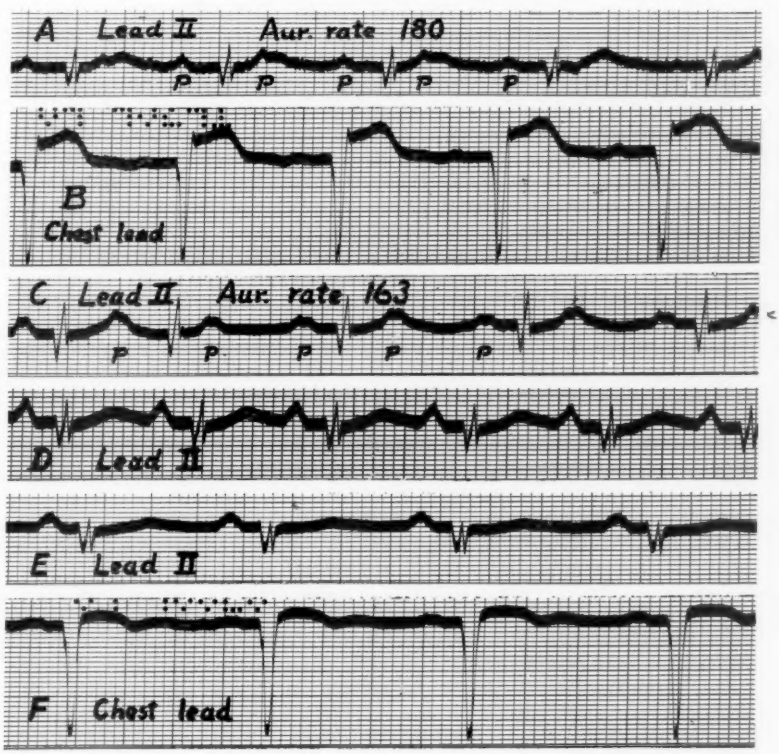

Fig. 17.—Case 17. *A*, May 13, 1942. Lead II. Auricular paroxysmal tachycardia with 2:1 A-V block. Auricular rate, 180. *B*, May 13, 1942. Precordial lead showing the changes of recent myocardial infarction. *C*, May 15, 1942, 2:15 P.M. Lead II. Auricular paroxysmal tachycardia with partial A-V block, usually 2:1. Auricular rate 163. Note the change in the form of the P waves. *D*, May 15, 1942, 4:50 P.M. Lead II. Normal rhythm. *E*, May 20, 1942. Lead II. Normal rhythm. Note the change in the form of the P waves. *F*, May 20, 1942. Precordial lead showing the expected progression of the changes accompanying myocardial infarction.

The first electrocardiogram (Fig. 17, *A*) was obtained May 13, 1942, the day after admission. It showed auricular paroxysmal tachycardia with 2:1 A-V block; the auricular rate was 180. Precordial leads showed changes suggesting very recent myocardial infarction (Fig. 17, *B*). On May 15, at 2:15 P.M. (Fig. 17, *C*), the auricular paroxysmal tachycardia was still present, with 2:1 A-V block most of the

time, and an auricular rate of 163. The auricular deflections were somewhat different in form from those of the previous curve. At 4:50 P.M. of the same day, normal rhythm was present, and the rate was 107 (Fig. 17, *D*). On May 20, 1942 (Fig. 17, *E*), normal rhythm was still present; the auricular deflections were different in form from those of the previous curve, and the rate was slower. Precordial leads showed the expected progression of the changes of myocardial infarction (Fig. 17, *F*).

CASE 18.—A white man, 45 years of age, was a patient in the hospital from July 5 to 15, 1940. Four years previously he had experienced sudden, severe pain beneath the sternum which persisted for four hours and was relieved by morphine. After that he was subject to substernal pain upon slight effort. For about nine months he had been dyspneic upon mild exertion and sometimes at rest. The breathing was often noisy. Cough had been present for four months. He was found to be allergic to house dust and several other substances, and was given epinephrine by nebulizer and ephedrine by mouth. There had been no edema of the extremities. Examination showed slight cardiac enlargement, presystolic gallop rhythm, and many wheezing, musical, and crackling râles in the lungs. The blood pressure was 130/94. He was given rest and digitalis, and improved remarkably.

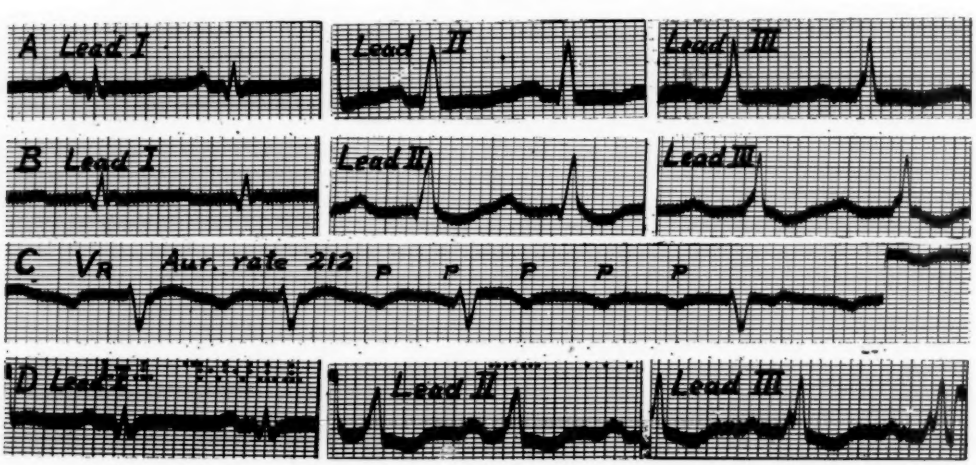

Fig. 18.—Case 18. *A*, July 6, 1940. Leads I, II and III. Normal rhythm. *B*, June 2, 1942. Leads I, II, and III. Auricular paroxysmal tachycardia with 2:1 A-V block. The auricular tachycardia is not readily apparent in these leads. *C*, June 2, 1942. Right arm potential (right arm electrode paired with the central terminal) taken a few seconds after *B*. The auricular tachycardia is clearly revealed during the short periods of 3:1 A-V block. *D*, June 9, 1942. Leads I, II, and III. Normal rhythm.

After being free from symptoms for six months, he began having shortness of breath again. In October, 1941, the substernal pain recurred, and thereafter orthopnea and edema of the ankles developed. He continued taking digitalis regularly. On May 25, 1942, he had an attack of tachycardia which was abrupt in onset and termination, lasted one hour, and was accompanied by substernal pain. He returned to the hospital June 1, 1942. Examination showed a dyspneic, apprehensive man with a severe, nonproductive cough. There were many musical and crepitant râles in the lungs. The heart was slightly enlarged, and gallop rhythm was present. The blood pressure was 152/118. There was slight edema of the ankles.

On the second hospital day (June 2, 1942), he developed tachycardia, accompanied by substernal pain. The heart rate was 160; it was slowed temporarily by pressure upon the left carotid sinus, but the tachycardia returned promptly upon cessation of the pressure. On June 4 the pulse was slower and the tachycardia had ceased after persisting for two days. There was, however, no other change in the patient's condition. He gradually improved.

The electrocardiagrams on the first admission showed changes suggestive of old myocardial infarction (Fig. 18, *A*). On June 2, 1942, the curve showed auricular paroxysmal tachycardia with an auricular rate of 212 and partial A-V block, usually 2:1, sometimes 3:1 (Fig. 18, *B* and *C*). Normal rhythm was present on June 4 and persisted (Fig. 18, *D*).

COMMENT

Clinical Features.—Our interest in auricular paroxysmal tachycardia with A-V block was aroused by seeing 7 patients with this disturbance in the brief period of ten months, from October, 1937, to August, 1938. A review of 100 unselected cases of auricular paroxysmal tachycardia revealed 8 additional cases in which there was A-V block. The essential data in one additional case were supplied by Dr. John Parkinson (Case 1). The last 2 cases are of interest because of the associated myocardial infarction. In 8 of these 18 cases the tachycardia was the outstanding symptom, and in 5 it caused moderate to marked disability. In 4 other cases the tachycardia, although not the chief difficulty, was of importance in that it contributed to the disability of the patients. In the remaining 6 cases there was no disability, or the abnormal rhythm was merely an incident in the course of other more important conditions.

The degree of disability experienced by these patients is often greater than that which occurs with the common type of auricular paroxysmal tachycardia. In 29 cases it was possible to estimate the degree of disability. It was marked in 10, moderate in 7, and slight in 6. There was no apparent disability in 2, and in 4 others the abnormal rhythm was merely an incident of relatively minor importance in the course of some other illness. In general, the patients with organic heart disease and those with attacks of longer duration suffered more pronounced disability than the others (see Table I). Two patients developed acute edema of the lungs; both of these had organic heart disease. Another patient without organic heart disease died of cardiac failure caused by paroxysmal tachycardia which had been present almost continuously for three months.

In auricular paroxysmal tachycardia with A-V block, the duration of the attacks is often longer than in the common type of auricular paroxysmal tachycardia. Of the 17 previously reported cases, in 8 the attacks lasted several days; the longest was ninety-four days. Of our 18 patients, 13 had attacks lasting two days or longer. Three of these are known to have had attacks lasting twenty-six, sixty, and thirteen days, respectively. On the other hand, in 3 of the previous cases and in 3 of our own there were brief attacks which lasted only a few minutes.

The auricular rate is usually between 165 and 200 per minute.

Faster and slower rates sometimes occur. Four patients showed, at times, rates of 121, 120, 120, and 129 per minute, respectively. In one of these (Case 15) the slowing was caused by digitalis, and in another (Case 17) by assuming the recumbent posture, whereas in our Case 4 it was attributed to quinidine. Three of our other patients showed auricular rates of 136, 137, and 130 per minute, respectively, and in one of these the slowing was caused by quinidine (Case 6). Very rapid auricular rates are sometimes encountered. Lewis' patient[1] had a rate of 290 per minute. The first of the patients of Sprague and White[6] showed a rate of 270 upon one occasion. Two of our patients had, at times, rates of 235 and 250 per minute, respectively. In some cases the auricular rate shows rather pronounced variations, usually in response to drugs.

The onset and termination of the abnormal auricular activity have been recorded graphically in several instances. They were abrupt, just as in paroxysmal tachycardia without A-V block. The case reported by Maddox[11] is exceptional in that the attack of tachycardia terminated by gradual slowing of the rate over a period of several days. In this and in many other respects it resembled that reported by Field, Barker, and Alexander.[15]

As a rule there is an abrupt transition from normal rhythm to paroxysmal tachycardia at the onset, and from paroxysmal tachycardia to normal rhythm at the termination of the attacks. In Dock's case,[8] after 5 Gm. of digitalis in sixteen days, the mechanism changed to atrioventricular bradycardia with reciprocating rhythm. In Brown's patient,[10] after large amounts of digitalis, the mechanism changed from auricular paroxysmal tachycardia to auricular fibrillation, and then to normal rhythm. One of our patients (Case 10) had auricular paroxysmal tachycardia with A-V block at a time when he was overdigitalized. Shortly after the digitalis was stopped the mechanism changed to auricular fibrillation, and then to normal rhythm (Fig. 10). Another patient (Case 12) was likewise overdigitalized when the paroxysmal tachycardia was present. On the following day the rhythm changed to auricular fibrillation, which persisted (Fig. 12). Although the transitions were not recorded, it seems highly probable that in these 3 cases the auricular paroxysmal tachycardia changed directly to auricular fibrillation without intervening normal rhythm. Spontaneous transitions from paroxysmal tachycardia to auricular flutter or fibrillation have been recorded, as have changes from flutter or fibrillation to paroxysmal tachycardia. Parkinson and Mathias[16] observed a patient with auricular paroxysmal tachycardia whose rate increased progressively until there was a gradual transition to auricular flutter. Records were obtained by Carr[17] on a patient with many short paroxysms of tachycardia arising in the A-V node who showed auricular flutter for a few seconds at the onset and termination of the attacks. This patient had received moderate amounts of digitalis. Lewis[18] has reported a case

in which auricular fibrillation apparently changed to auricular paroxysmal tachycardia; the record of the transition was not published. It is possible that digitalis was responsible for the change to auricular fibrillation in the cases mentioned above, although in other cases of auricular paroxysmal tachycardia digitalis has restored normal rhythm without intervening auricular flutter of fibrillation.

In our Case 2 auricular flutter and auricular fibrillation were observed at different times, but it is not known whether there were transitions from either of these abnormal rhythms to paroxysmal tachycardia or vice versa. It is of interest that, of 100 unselected cases of auricular paroxysmal tachycardia, in only 5 was the patient known to have had auricular flutter or fibrillation, and that 3 of these had partial A-V block.

In some of the cases in which the onset or termination of an attack was recorded there was 1:1 ventricular response; the A-V block appeared during the course of the paroxysm. In other instances the block was present at the very beginning of the attack or continued to its very end.

In most cases the A-V block was fairly persistent or was maintained by digitalis, but 1:1 response could be brought on by exertion or occurred when digitalis was not taken. In some instances the patient was aware of the abnormal cardiac mechanism only during the periods of 1:1 ventricular response, which began and ended suddenly. The occurrence of 1:1 response increased the severity of the symptoms and accounted for the disability of some of the patients. Others, however, were incapacitated even with ventricular rates of about 100 per minute. In a few cases the block was transient and of short duration.

Patients with auricular paroxysmal tachycardia and partial A-V block are often very resistant to treatment. This is reflected in the long duration of some of the attacks. Pressure upon the carotid sinus restored normal rhythm only in Case 12 (Mackinnon). In many other cases it failed to do so. It commonly increased the degree of block and slowed the ventricles temporarily.

Digitalis was beneficial in 7 of the 17 previously reported cases; normal rhythm returned soon after the administration of full doses. In Cases 11 and 15 it was given without benefit, and, in the other 8 cases, it was apparently not used. Digitalis was given in 16 of our 18 cases, and in only 7 did it appear beneficial. In only 4 of these did normal rhythm return soon after the administration of the drug. In the other 3 it increased the degree of A-V block and prevented, in part, the occurrence of 1:1 response, so that the patients were improved symptomatically, but normal rhythm returned several days or weeks after full digitalization, and could not be attributed definitely to the drug. In some of the other cases digitalis may have been at least partly responsible for the partial A-V block, but did not appear to be beneficial in other respects. Digitalis sometimes causes considerable slowing of the auricular rate (Cases 4 and 14).

Quinidine was given in 5 of the previously reported cases. It prevented the attacks of paroxysmal tachycardia in Case 17 (Fine and Miller), but was without value in Cases 5, 6, 7, and 15. Quinine likewise was given in 5 of the previously reported cases. It restored normal rhythm in 3 (Cases 2, 8, and 10), but was without benefit in Cases 4 and 15. Quinidine was given to 8 of our patients. It restored normal rhythm in Cases 6, 7, and 9. In Cases 6 and 7, its continued use definitely prevented the return of the tachycardia, and in Case 9 it was probably of some benefit in preventing recurrences. In Cases 1, 2, 3, 4, and 15, quinidine was given without apparent benefit, although it slowed the auricular rate in Cases 3 and 4. There was no adequate explanation for death in Case 6; the patient had been taking quinidine sulfate in a dose of 0.3 Gm. 3 times daily for several days, but it is scarcely possible that this could have been responsible. Quinine was used in Case 2 without apparent benefit. Both quinidine and quinine sometimes cause conspicuous slowing of the auricular rate (Case 4 and our Cases 3, 4, and 6).

Mecholyl was given to 3 of our patients. It caused transient slowing of the ventricles by increasing the degree of block, but did not restore normal rhythm.

Electrocardiograms.—In the common type of auricular paroxysmal tachycardia the P waves are often almost indistinguishable because they are very small or flat, or because, in addition to being small, they fall upon some part of the ventricular complex. In about one-sixth of the cases the P waves are inverted. In only about 30 per cent are they upright and approximately similar in form to the P waves of normal rhythm. In auricular paroxysmal tachycardia with A-V block, about 60 per cent of the patients have P waves which are upright or largely so, and resemble, perhaps not exactly, but at least fairly closely, the P waves of normal rhythm. When P is diphasic or notched, it often shows a similar configuration during normal rhythm. The similarity of the P waves during the tachycardia and during normal rhythm is shown in 6 of the previously reported cases (Cases 3, 6, 7, 8, 9, and 15), and is well illustrated in ten cases of the present series (Cases 1, 2, 3, 5, 7, 10, 11, 13, 16, and 18). This indicates that in these cases the paroxysmal tachycardia had its origin near the sinoauricular node. It is possible that A-V block is more likely to occur in such cases, as compared with cases in which the form of P suggests an origin near the auriculoventricular node. In Cases 12 and 14 the P waves were upright during the tachycardia, but no tracings of normal rhythm were obtained for comparison. In 6 of the previously reported cases (Cases 2, 4, 5, 11, 14, and 17) and in 6 cases of our series (Cases 4, 6, 8, 9, 15, and 17) the P waves during the tachycardia were quite different from the P waves of normal rhythm. In Cases 4 and 8, P was very small during the tachycardia, whereas, in Cases 6 and 15, it was inverted. In Cases 9 and 17, the P waves were upright during the tachycardia but quite different in form from those of normal rhythm.

When the P waves are small or indistinct in the standard leads, it may not be possible to identify them with certainty, or to ascertain what type of arrhythmia is present. Under such circumstances it may be helpful to employ chest leads. By leading from two precordial contacts, one over the upper part of the sternum and the other over the ensiform, it is usually possible to record large auricular waves which are readily identified. This is well illustrated in Case 4 (Fig. 4). Esophageal leads may be even more helpful, for they invariably yield very large auricular deflections when employed as described by Brown.[10] They may be especially helpful in distinguishing auricular paroxysmal tachycardia from flutter. In the former the auricular deflections are separated, during A-V block, by periods of electrical quiescence, in which the curve is at rest on the base line, whereas, in the latter, the curve is never at rest, but shows continuous changes in electrical potential (Figs. 2 and 7). These observations confirm those of Brown. The use of esophageal leads, however, imposes some hardship upon the patient.

The partial A-V block seems to be caused by the abnormally high auricular rate, at least to a considerable degree. In some of the patients, digitalis was a contributing factor. In none of the previously reported cases was there abnormal prolongation of the P-R interval during normal rhythm, although in several it was 0.20 second. In Case 2 (Singer and Winterberg), complete block persisted after the termination of the paroxysmal tachycardia. In the present series, likewise, the P-R interval was nearly always normal during normal rhythm, but there were a few exceptions. In Case 4 it was 0.22 second at times, but large amounts of digitalis had been given. In Case 10 the P-R interval was 0.20 second several months before the tachycardia occurred and before digitalis was given; when normal rhythm returned after the paroxysmal tachycardia it was 0.28 second, but the patient had been overdigitalized. One patient (Case 13) had a P-R interval of 0.24 second on the day when normal rhythm returned, and he had received no drugs; four months later it was 0.19 second.

The occurrence of auricular flutter and auricular fibrillation in Cases 2, 10, and 12 has been mentioned. Two other patients (Cases 7 and 8) showed abnormal auricular mechanism after cessation of the paroxysmal tachycardia; they yielded curves in which no auricular waves could be identified. It was thought that they might represent A-V nodal rhythm, but no special leads were employed and no large venous pulsations were observed, and it is possible that there was auricular standstill. The ventricles were beating regularly at normal rates. In several cases normal rhythm was disturbed by occasional auricular extrasystoles. One patient (Case 17) showed changes in the form of the P waves, both during the paroxysm of tachycardia and during normal rhythm shortly after the cessation of the attack.

The Mechanism of Auricular Paroxysmal Tachycardia.—Auricular paroxysmal tachycardia with partial A-V block resembles auricular flutter in many respects. It resembles flutter much more closely than does the common type of auricular paroxysmal tachycardia. The similarities extend beyond the presence of the partial block and the relatively long duration of some of the attacks. Quinidine and quinine often slow the auricular rate in auricular paroxysmal tachycardia and always do so in auricular flutter. In a few cases, digitalis in large amounts apparently converted auricular paroxysmal tachycardia into auricular fibrillation, a common occurrence in auricular flutter. In these cases, as in flutter, pressure upon the carotid sinus temporarily increases the degree of block and slows the ventricles, but almost never stops the attacks of abnormal rhythm. With respect to A-V block, the differences between auricular paroxysmal tachycardia and auricular flutter may be caused chiefly by the differences in the auricular rates in the two conditions.

In spite of the resemblances between auricular paroxysmal tachycardia with partial A-V block and auricular flutter, the two conditions differ from each other in several important respects. Digitalis sometimes slows the auricular rate in the former, whereas, in the latter, it has little effect, or induces auricular fibrillation. Pressure upon the carotid sinus restored normal rhythm in Case 13 (Mackinnon); it never does so in auricular flutter. In the common type of paroxysmal tachycardia, normal rhythm is often restored by pressure upon the carotid sinus. An important difference between auricular paroxysmal tachycardia with partial A-V block and auricular flutter is that in the former the auricular deflections are separated by periods of electrical quiescence, during which the curve is at rest on the base line, whereas, in the latter, the curve is never at rest, but shows continuous changes in electrical potential. This is apparent quite commonly in standard leads, usually in precordial leads, and always in esophageal leads.

If auricular paroxysmal tachycardia is caused by re-entry of the impulse, it must be a special kind of circus rhythm, differing from that of auricular fibrillation. Circus rhythm involving as part of the path of the circulating excitation wave either the sinoauricular node or the auriculoventricular node could account for most, if not all, of the features of auricular paroxysmal tachycardia. This possibility has been discussed briefly by Ashman and Hull.[19] In our opinion, circus rhythm can account for auricular paroxysmal tachycardia only if it involves one of the nodes, or if the amount of muscle in some part of the main circus path is so small that its action potential cannot be recorded by ordinary methods. In a subsequent communication we hope to present additional evidence bearing upon this problem, and to discuss it at greater length.

SUMMARY

1. Seventeen previously reported cases of auricular paroxysmal tachycardia with auriculoventricular block are reviewed, and eighteen additional cases are reported.

2. This arrhythmia may occur at almost any age, and in persons with otherwise normal hearts or with organic heart disease.

3. The attacks are often of long duration, i.e., they commonly last several days or longer.

4. High-grade disability is common in patients with organic heart disease, but sometimes occurs in those with otherwise normal hearts. One patient without significant organic heart disease died of cardiac exhaustion and failure attributable entirely to the long continued tachycardia.

5. In some cases the auricular deflections of the electrocardiogram are small or not readily apparent in limb leads. In such instances precordial or esophageal leads are especially valuable because they yield prominent auricular waves and thus permit the identification of the arrhythmia. Such curves are quite different from those of auricular flutter, in that the auricular deflections are separated by periods of electrical quiescence, with the curve at rest on the base line.

6. Digitalis in large amounts often restores normal rhythm. Quinidine and quinine are somewhat less effective, but sometimes restore normal rhythm, occasionally even when digitalis has failed to do so. Pressure upon the carotid sinus rarely terminates the paroxysms; it was successful in only one case (Mackinnon[9]). Mecholyl and acetylcholine have been ineffectual. Some patients may not respond to any of these measures; in one such instance normal rhythm returned spontaneously after a period of rest in bed, whereas, in another, death resulted from cardiac exhaustion caused by the prolonged tachycardia.

7. Auricular paroxysmal tachycardia with partial A-V block resembles auricular flutter in many respects, but differs from it in some important particulars. Most of the features of auricular paroxysmal tachycardia can be accounted for by circus rhythm involving either the sinoauricular node or the auriculoventricular node.

REFERENCES

1. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw and Sons, Ltd.
2. Koplik, H.: Paroxysmal Tachycardia in Children, Am. J. M. Sc. **154**: 834, 1917.
3. Singer, R., and Winterberg, H.: Chinin als Herz- und Gefäszmittel, Wien. Arch. f. inn. Med. **3**: 329, 1922.
4. Gallavardin, L.: Tachycardia Paroxystique a Forme Arythmique par Trouble de la Conductibilite Auriculo-Ventriculaire. Simulation d'un Rhythme Atrio-Ventriculaire, Arch. d. mal. du coeur **16**: 117, 1923.
5. Lenhartz, H., and Samet, B.: Beitrag zur Kenntnis der Tachykardie, Wien. Arch. f. inn. Med. **9**: 71, 1924.
6. Sprague, H. B., and White, P. D.: Heart-Block During Auricular Paroxysmal Tachycardia (Clinical Observations on Three Cases), M. Clin. North America **8**: 1855, 1925.

7. Wenckebach, K. F., and Winterberg, H.: Die unregelmässige Herztätigkeit, Leipzig, 1927, Wilhelm Engelmann.
8. Dock, W.: The Reciprocal Rhythm. Report of a Case in Which Auricular Tachycardia With Partial A-V Dissociation and Atrioventricular Bradycardia, With Reciprocating Rhythm, Were Present, Arch. Int. Med. **41**: 745, 1928.
9. Mackinnon, A. V.: The Rhythm of Paroxysmal Tachycardia. An Electrocardiographic Study, Quart. J. Med. **27**: 1, 1934.
10. Brown, W. H.: A Study of the Esophageal Lead in Clinical Electrocardiography, AM. HEART J. **12**: 307, 1936.
11. Maddox, K.: Auricular Paroxysmal Tachycardia (Possibly Nomotopic) With Variable Auriculo-Ventricular Conduction Time, AM. HEART J. **14**: 183, 1937.
12. Maarssø, C.: Et tilfaelde af paroxysmatisk tachycardi med partielt atrioventrikulaert blok hos et 8 aars barn, Hospitalstid. **8**: 1140, 1937.
13. Fine, M. J., and Miller, R.: Orthostatic Paroxysmal Auricular Tachycardia With Unusual Response to Change of Posture, AM. HEART J. **20**: 366, 1940.
14. Katz, L. N.: Electrocardiography, Philadelphia, 1941, Lea and Febiger.
15. Field, H., Jr., Barker, P. S., and Alexander, J.: Unusual Sinus Tachycardia With Observations on Vagal Activity, AM. HEART J. **9**: 298, 1934.
16. Parkinson, John, and Mathias, H. H.: Tachycardia of Auricular Origin and Flutter With Phasic Variation in Auricular Rate and in Conduction, Heart **6**: 27, 1915.
17. Carr, F. B.: Auriculoventricular Nodal Paroxysmal Tachycardia and Auricular Flutter. Case Report, AM. HEART J. **7**: 668, 1932.
18. Lewis, T.: Auricular Fibrillation and Its Relationship to Clinical Irregularity of the Heart, Heart **1**: 306, 1910.
19. Ashman, R., and Hull, E.: Essentials of Electrocardiography, ed. 2, New York, 1941, The Macmillan Co.

AURICULAR PAROXYSMAL TACHYCARDIA WITH ALTERNATION OF CYCLE LENGTH

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THE purpose of this paper is twofold: first, to describe an irregularity of the heartbeat which occurred during attacks of auricular paroxysmal tachycardia and was characterized by alternation of the cycle length, and, second, to discuss its significance with reference to the mechanism of auricular paroxysmal tachycardia.

As a rule, auricular paroxysmal tachycardia displays a high degree of regularity. This has been emphasized by Feil and Gilder,[1] who measured 11 to 18 consecutive ventricular cycles in the electrocardiograms of eight patients with auricular paroxymal tachycardia. The maximal variation in the length of the ventricular cycles, not necessarily consecutive, ranged in different cases from 0.0071 to 0.0358 second, and was usually less than 0.0099 second; the average never exceeded 0.01 second. Two of their patients showed very slight alternation in the lengths of the cycles, but they did not comment upon this. Their measurements, in seconds, were as follows: Case R 742 (rate, 214 per minute), 0.2836, 0.2810, 0.2833, 0.2770, 0.2813, 0.2808, 0.2838, 0.2798, 0.2848, 0.2828, 0.2801, 0.2788, 0.2770, 0.2813, 0.2851, and 0.2752. Case G. 1843 (rate, 185 per minute), 0.3161, 0.3278, 0.3132, 0.3345, 0.3126, 0.3434, 0.3076, 0.3293, 0.3273, 0.3328, 0.3242, 0.3311, 0.3138, 0.3343, 0.3095, 0.3331.

In an interesting case reported by White[2] there were many short attacks of auricular paroxysmal tachycardia, with abrupt onset and termination, but with acceleration at the beginning and slowing toward the end of the paroxysms. During the tachycardia the P wave resembled the P of normal rhythm; it was upright in Lead II. The author did not comment on the alternation of cycle length shown by his measurements, which were as follows: (a) beginning of attack—0.407, 0.425, 0.384, 0.323, 0.316, 0.325, 0.308, 0.327, 0.317, 0.336, and 0.316 second; (b) at height of paroxysm—0.316, 0.323, 0.310, and 0.326 second (rate, 188).

Strong and Levine[3] have emphasized the regularity of auricular paroxysmal tachycardia as contrasted with the irregularity of ventricular paroxysmal tachycardia. They measured the ventricular cycles during an attack of auricular paroxysmal tachycardia which occurred in one of their patients. The heartbeat was regular to a very high

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TABLE I

THE ESSENTIAL FEATURES OF CASES OF AURICULAR PAROXYSMAL TACHYCARDIA WITH ALTERNATION OF CYCLE LENGTH

CASE	AGE	SEX	FORM OF P WAVE*			MAXIMUM VARIATION† (SECONDS)	MAXIMUM VARIATION IN CONSECUTIVE CYCLES† (SECONDS)	RATE	CLINICAL DIAGNOSIS
			LEAD I	LEAD II	LEAD III				
Feil and Gilder[1]						0.008 0.036	0.006 0.036	214 185	
White[2]	21	M	+	+	+	0.028	0.019	188	No organic heart disease
Strong and Levine[3]			inverted	(lead not stated)		0.01	0.01	148	
1	52	M	±	−	−	0.054	0.054	114	Arteriosclerosis, aortic stenosis, congestive failure
2	19	M	−	+	+	0.095	0.095	136	No organic heart disease
3	37	M	±	±	±	0.049	0.048	184	Mitral stenosis and aortic regurgitation
4	61	F	±	±	±	0.036	0.025	175	Hypertension, congestive failure
5	70	M	±	±	±	0.056	0.051	132	Arteriosclerosis
6	36	F	±	±	±	0.038	0.034	195	No organic heart disease
7	19	M	±	±	±	0.028	0.022	158	No organic heart disease
8	79	M	±	±	±	0.022	0.022	120	Hypertension, arteriosclerosis, cardiac enlargement
9	40	F	±	±	±	0.022	0.021	222	Hyperthyrodism, diabetes mellitus
10	46	M	±	±	±	0.036	0.024	150	No organic heart disease

*Upright, +; inverted, −; diphasic or intermediate, ±.

†The irregularity which sometimes occurred at the beginning and ending of attacks is not included. In our Cases 1 and 2 the figures are for the auricular cycles, and, in all other cases, ventricular cycles.

degree, but there was a short period of slight alternation in cycle length which they did not mention or discuss. Their measurements, in seconds, were as follows: 0.41, 0.405, 0.405, 0.405, 0.405, 0.405, 0.405, 0.405, 0.41, 0.405, 0.41, 0.41, 0.41, 0.405, 0.41, 0.40, 0.41, and 0.405 (rate, 148).

Katz[4] recently published a short record in which he called attention to alternation in length of auricular and ventricular cycles and P-R intervals. The longer ventricular cycles accompanied the longer auricular cycles, and the P-R intervals were longer after the shorter auricular cycles. Measurements of the tracing and clinical data were not given.

Mackinnon[5] has pointed out that, in auricular paroxysmal tachycardia, the heartbeat is often somewhat irregular, but in none of his fifteen cases was there alternation of cycle length.

Careful inspection of the electrocardiograms in one hundred unselected cases of auricular paroxysmal tachycardia from our files revealed ten cases in which there was, in some of the curves, a slight irregularity of a type characterized by alternation in the lengths of the cycles. This irregularity, although slight, was apparent to the unaided eye. Its presence was confirmed by accurate measurements with a Lucas comparator. In only two of our cases were the auricular deflections sufficiently sharp to permit accurate measurements of the P-P intervals. In these the auricular cycles, the ventricular cycles, and the P-R intervals were measured. In the remaining cases only the ventricular cycles were measured. In all instances the beginning of the R wave and, in the two cases in which there were sufficiently sharp auricular deflections, the beginning of the P wave were the points employed in making the measurements. The essential features of our cases, and of those discovered in the literature, are given in Table I.

CASE REPORTS

Case 1.—A white man, 52 years of age, was first seen Jan. 27, 1933. He had advanced arteriosclerosis, aortic stenosis, and pronounced cardiac enlargement. He improved temporarily, but later his symptoms progressed and he developed angina pectoris of effort, attacks of tachycardia, pulsus alternans, and, finally, congestive cardiac failure. He died April 5, 1936. The autopsy showed advanced atherosclerosis, with calcification of the aorta, aortic stenosis with calcification, pronounced cardiac hypertrophy (the heart weighed 890 grams), and chronic passive congestion of the lungs and abdominal viscera. An electrocardiogram taken when the rhythm was normal is shown in Fig. 1, and an attack of auricular paroxysmal tachycardia is illustrated in Fig. 2. The measurements of the auricular and ventricular cycles and of the P-R intervals are given in the same figure. Although the patient had previously shown pulsus alternans, no alternation in the force of the pulse was observed at the time of the attack of paroxysmal tachycardia. The alternation in cycle length was not obvious on auscultation.

Case 2.—A 15-year-old boy was first seen in June, 1926, because of attacks of tachycardia. These continued to occur from time to time, and he returned to the clinic at intervals until July, 1935. Repeated examinations revealed no evidence of organic heart disease. A number of electrocardiograms were taken. Some of these were entirely normal. Others showed auricular extrasystoles. Still other curves

displayed auricular paroxysmal tachycardia which was sometimes of short, at other times of longer, duration. The paroxysm depicted in Fig. 3 occurred Sept. 12, 1930. The measurements of the auricular and ventricular cycles and of the P-R intervals are given in this figure. The alternation of cycle length is complicated by the occasional occurrence, usually every fourth beat, of an especially short cycle, which does not, however, interrupt the alternation.

In these two cases the auricular cycles, the ventricular cycles, and the P-R intervals alternated in length. The longer ventricular cycles corresponded to the longer auricular cycles, and the longer P-R intervals usually, but not invariably, followed the shorter auricular cycles. Because of the alternation of the P-R intervals, the R-R intervals varied less than the P-P intervals.

In the remaining cases the auricular deflections were not sufficiently sharp to permit accurate measurement; only the ventricular cycles were measured.

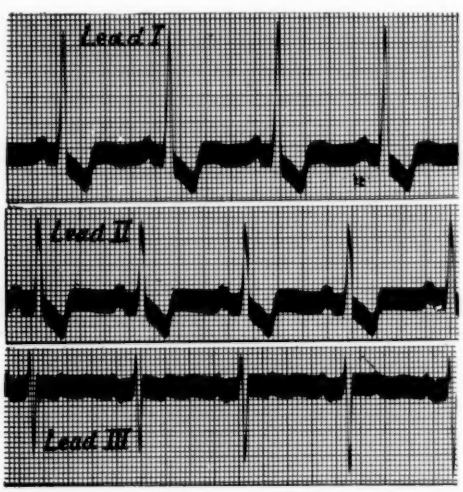

Fig. 1.—Case 1. Leads I, II, and III. Normal rhythm.

Case 3.—A white man, 37 years of age, was first seen Feb. 26, 1929. He had rheumatic heart disease, with mitral stenosis, aortic regurgitation, and cardiac enlargement. He complained chiefly of attacks of tachycardia, but also suffered from shortness of breath and occasional swelling of the ankles. The attacks of tachycardia were not stopped or prevented by quinidine, nor were they favorably influenced by thyroidectomy, which was performed because of mild hyperthyroidism. Digitalis in full doses apparently prevented the attacks for a year, but they returned. Two attacks were stopped by quinine intravenously, others by pressure upon the carotid sinus. Finally, the patient developed auricular fibrillation and severe cardiac failure, and died June 19, 1931. There was no autopsy. Many electrocardiograms were obtained, some during normal rhythm and others during paroxysms of auricular tachycardia. In one of these there was alternation of cycle length (Fig. 4). In this case, too, the variation in cycle length was complicated. The alternation of long and short cycles was interrupted by cycles of intermediate length which usually occurred every fifth beat, following the shorter, and preceding the longer, cycles.

Case 4.—The patient was a white woman, 61 years of age, with a blood pressure of 220/120, hypertensive heart disease, cardiac enlargement, and congestive failure. She grew progressively worse, and died two weeks after admission. The autopsy

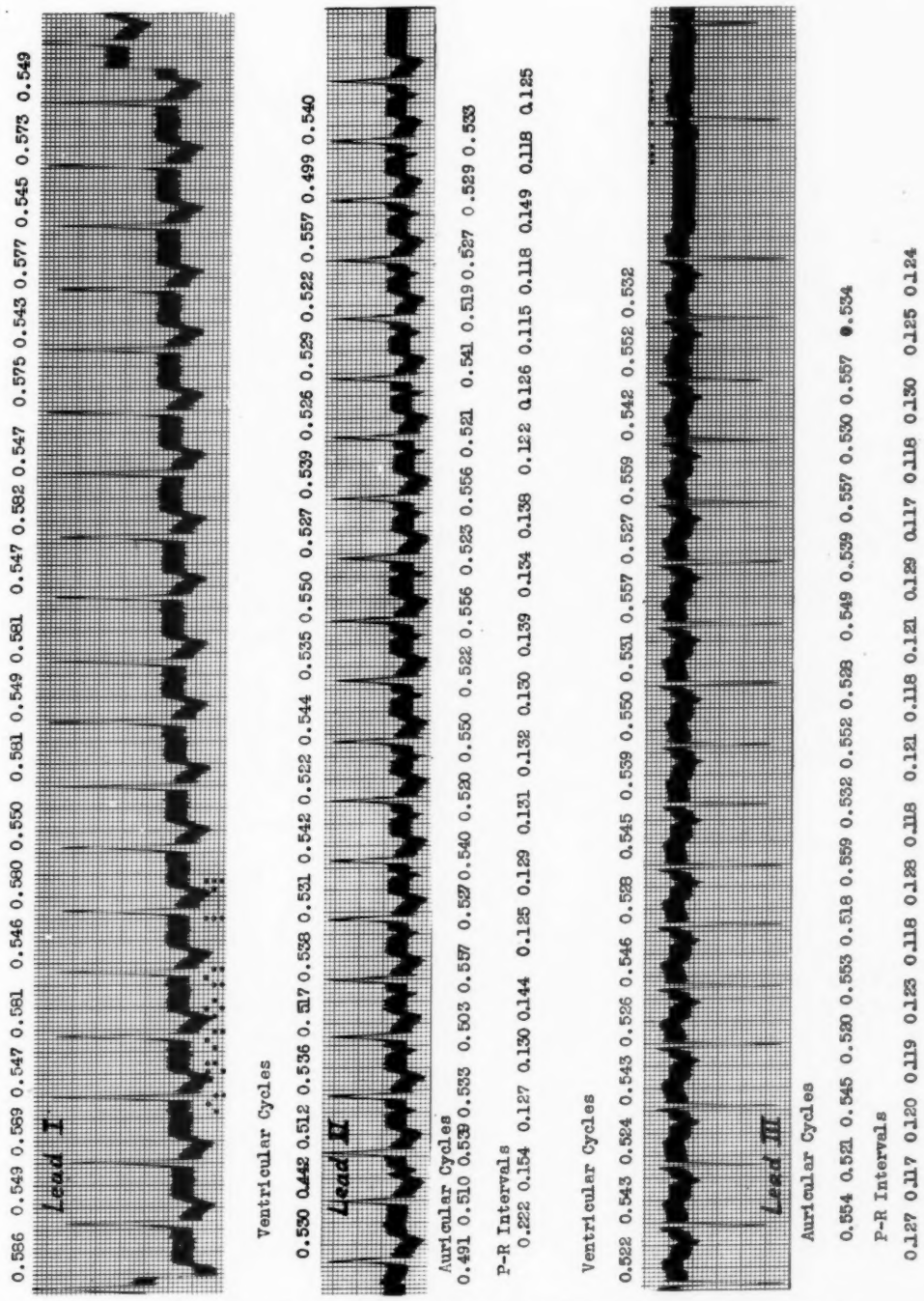

Fig. 2.—Case 1. Three standard leads. Auricular paroxysmal tachycardia. Measurements in seconds. In Lead I the ventricular cycle lengths are shown above; the auricular deflections are not sufficiently sharp to permit accurate measurements. Lead II shows one short paroxysm in its entirety. Lead III shows the end of a paroxysm. These curves show alternation in the lengths of the auricular and ventricular cycles and the P-R intervals.

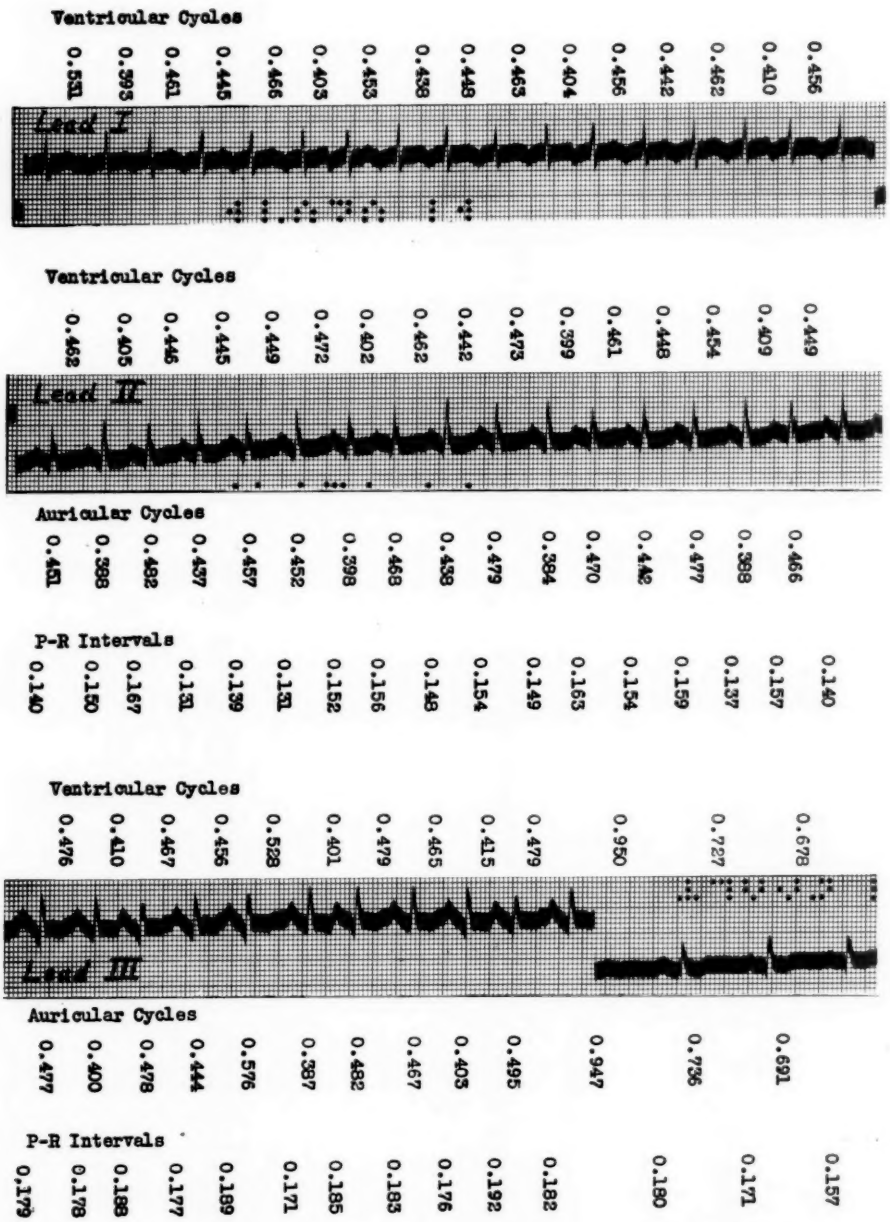

Fig. 3.—Case 2. Leads I, II, and III. Auricular paroxysmal tachycardia. Measurements in seconds. In Lead I the auricular deflections are not sufficiently sharp to permit accurate measurement. Lead III shows the termination of an attack. There is alternation in the lengths of the auricular and ventricular cycles and the P-R intervals.

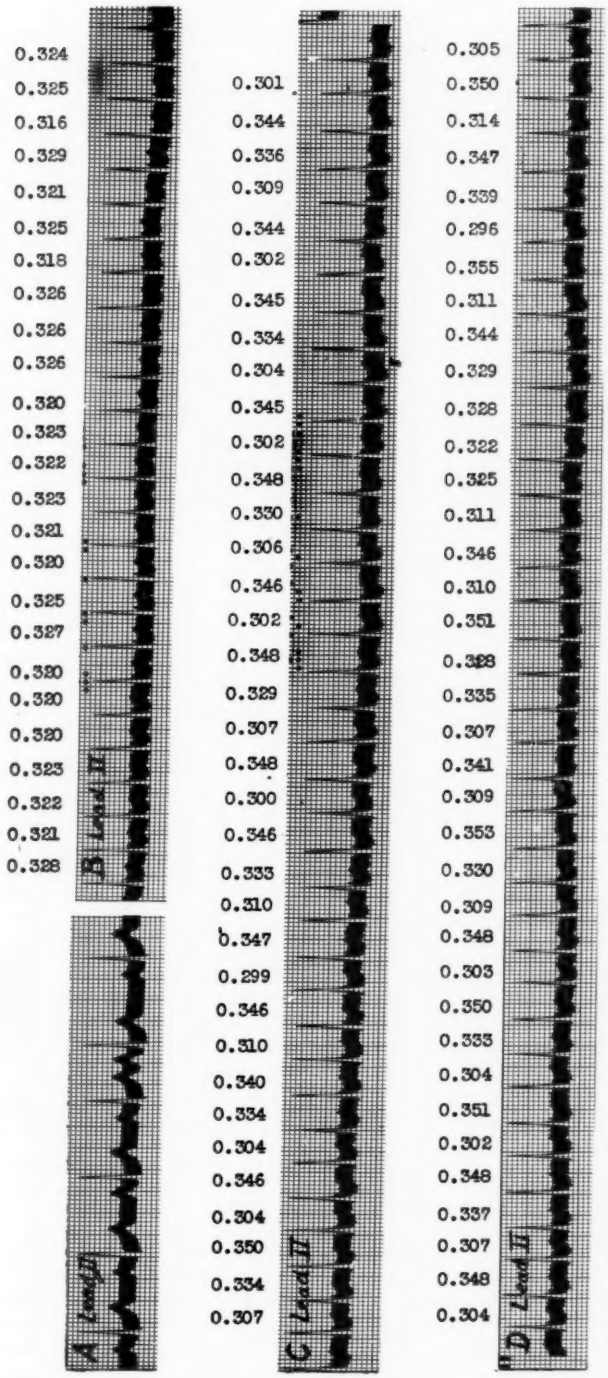

Fig. 4.—Case 3. Lead II. Ventricular cycle lengths, in seconds, are shown above the curves. The auricular deflections are not sufficiently sharp to permit accura e measurements. *A*. Normal rhythm with one auricular extrasystole. *B*. Auricular paroxysmal tachycardia, several hours after the onset of the attack. There is only transient, slight alternation of cycle length. *C*. Same attack six hours later. Alternation of cycle length is present. *D*. Same attack two minutes later, during the intravenous administration of 0.5 Gm. of quinine dihydrochloride. In *C* and *D* the alternation of cycle length is apparent; it is interrupted by occasional cycles of intermediate length, usually every fifth cycle.

showed advanced atherosclerosis, with calcium deposits in the aorta, cardiac hypertrophy (the heart weighed 410 grams), and chronic passive congestion of all organs. The only electrocardiogram which was obtained showed auricular paroxysmal tachycardia, a rate of 175, and alternation of cycle length. The alternation was interrupted by an extra long cycle at times, usually every fifth beat. The measurements of the cycle lengths, in seconds, are as follows: 0.324, 0.342, 0.338, 0.344, 0.352, 0.334, 0.343, 0.341, 0.345, 0.346, 0.345, 0.355, 0.335, 0.360, 0.346.

Case 5.—The patient was a 70-year-old white man who suffered from palpitation of the heart and shortness of breath upon slight exertion. He was overweight, but examination of the heart revealed no abnormality other than an arrhythmia. On auscultation this appeared to be caused by several extrasystoles in succession, followed by an abrupt change in rate from 80 to 146, with regular rhythm. Pressure upon the carotid sinus caused only slight slowing. Later, another attack of tachycardia was terminated by carotid sinus pressure. The electrocardiogram showed auricular paroxysmal tachycardia, with alternating long and short cycles. The variations in cycle length were sometimes very slight, and, at other times, quite pronounced; the alternation, however, was maintained. The measurements, in seconds, of the cycle lengths in one complete paroxysm from beginning to end are as follows: 0.394, 0.551, 0.432, 0.450, 0.455, 0.461, 0.447, 0.464, 0.447, 0.473, 0.444, 0.469, 0.441, 0.468, 0.447, 0.463, 0.456, 0.469, 0.442, 0.462, 0.436, 0.466, 0.441, 0.460, 0.437, 0.457, 0.432, 0.449, 0.434, 0.452, 0.428, 0.455, 0.427, 0.445, 0.425, 0.446, 0.431, 0.445, 0.423, 0.444, 0.418, 0.452, 0.417, 0.441, 0.429, 0.443, 0.414, 0.446, 0.428, 0.453, 0.413, 0.464, 0.419, 0.453, 0.426, 0.450, 0.422, 0.460, 0.421, 0.459, 0.418, 0.462, 0.421, 0.435, and 0.425.

Case 6.—A white woman, 36 years of age, was first seen in January, 1926. Since the age of 5 years she had suffered from attacks of tachycardia during which the heart beat regularly at rates varying from 184 to 214 per minute. The attacks lasted from a few seconds to twelve days, and occurred at intervals of a few minutes to three weeks. They were accompanied by a sensation of throbbing of the heart, shortness of breath and nervousness, and, when long continued, by abdominal discomfort, nausea, and vomiting. She sometimes fainted at the onset or at the termination of an attack. Between attacks the heart was often slow, and sometimes irregular. Examination showed frequent extrasystoles, but no other cardiac abnormality. The blood pressure was 120/80. The patient was seen a number of times during the next eleven years. Some of her attacks were stopped by pressure upon the carotid sinus, others by mecholyl. Digitalis and quinidine were given without benefit. During normal rhythm there were many ventricular extrasystoles. In one attack of auricular paroxysmal tachycardia the electrocardiogram showed alternation of cycle length. There was considerable variation of the R-R interval at the onset of the attack, and alternation did not appear for several beats. The measurements, in seconds, from the beginning of the paroxysm are as follows: 0.435, 0.285, 0.301, 0.303, 0.300, 0.302, 0.307, 0.304, 0.313, 0.305, 0.319, 0.305, 0.335, 0.307, 0.327, 0.301, 0.335, 0.308, 0.339, 0.309, 0.339, 0.308, 0.335, 0.317, 0.330, 0.314, 0.331, 0.317.

In the remaining cases there was considerable variation in the cycles, but no definite disturbance in the alternation of their lengths.

Case 7.—A 19-year-old white man was referred for an electrocardiogram only. No history was obtained and he was not examined. A year later, however, when he had measles, examination revealed no abnormality of the heart. The electrocardiogram (Fig. 5) showed paroxysmal tachycardia of supraventricular origin, with alternation of cycle length. The onset and termination of an attack were recorded. The tracing was exceptional in that the P waves of Lead III appeared to alternate in form. The possibility cannot be excluded that this was caused by

alternation in the form of the T waves. This possibility received some support from the presence of alternation in the amplitude of the R waves in Lead II, although there was no alternation in the form of the T waves in that lead or in the amplitude of the R waves in Lead III.

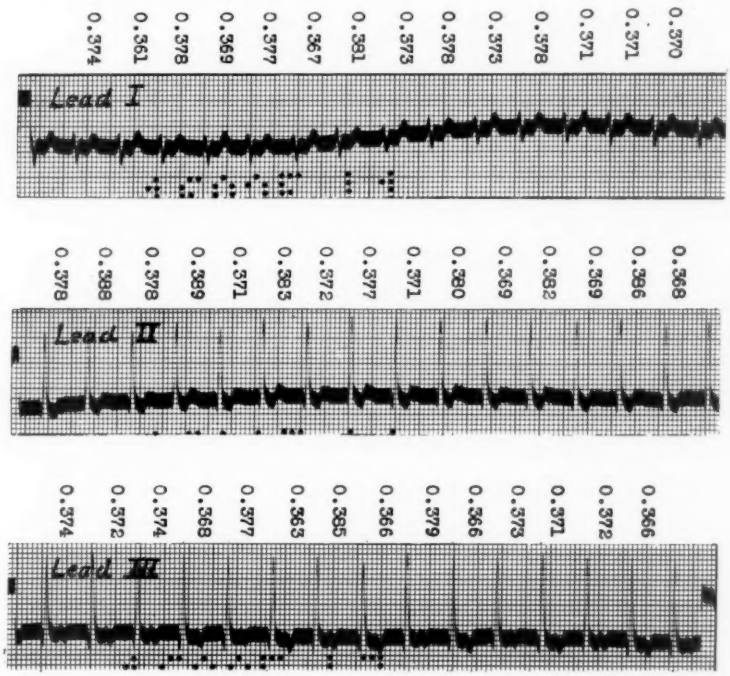

Fig. 5.—Case 7. Three standard leads. Auricular paroxysmal tachycardia, with alternation of ventricular cycle length. Measurements in seconds. There appears to be alternation in the form of the auricular deflections in Lead III.

Case 8.—The patient was a white man, 79 years of age. He had urinary obstruction caused by carcinoma of the prostate, and also hypertension (195/90), arteriosclerosis, cardiac enlargement, and mild congestive failure. He was observed to have many short attacks of tachycardia, with regular rhythm, and a rate of about 120 per minute. During the attacks there was pulsus alternans; alternate beats raised the systolic blood pressure to 150 and 130, respectively. Alternation of the cycle length was not detected clinically. The attacks were abrupt in onset and termination, and some of them were stopped by pressure upon the carotid sinus. Digitalis had no effect upon the attacks, but quinidine prevented them. Electrocardiograms showed paroxysmal tachycardia of supraventricular origin, of which there were sometimes many short attacks. When sinus rhythm was present auricular extrasystoles often occurred. During one attack of tachycardia there was alternation of cycle length; the measurements, in seconds, are as follows: 0.498, 0.506, 0.499, 0.516, 0.501, 0.515, 0.501, 0.515, 0.499, 0.517, 0.503, 0.518, 0.496, 0.517, 0.497, 0.514, 0.504, 0.517, 0.499.

Case 9.—The patient was a 40-year-old white woman who had had a goiter for seventeen years, symptoms of hyperthyroidism for two years, and diabetes for three months. She was undernourished and there was moderate, diffuse enlargement of the thyroid. There was no apparent abnormality of the heart. While the diabetes was being brought under control, hypoglycemia occurred, and epinephrine (1:1000,

0.6 c.c.) was given subcutaneously. After this an attack of tachycardia occurred. The electrocardiogram showed auricular paroxysmal tachycardia, with a rate of 222 and alternation of cycle length. The attack was stopped by pressure upon both eyes. A month later a typical paroxysm, with a heart rate of 188, occurred spontaneously; it lasted thirty minutes. In the curve which showed alternation of cycle length, measurements of the ventricular cycles gave the following values, in seconds: (Lead I) 0.263, 0.278, 0.264, 0.281, 0.265, 0.277, 0.266, 0.273, 0.271, 0.276, 0.266, 0.278, 0.268, 0.276, 0.265, 0.280. (Lead II) 0.263, 0.279, 0.259, 0.280, 0.262, 0.275, 0.264, 0.278, 0.261, 0.280, 0.261, 0.262, 0.278, 0.265, 0.279.

Case 10.—The patient was a 46-year-old American Indian. For six months he had suffered from shortness of breath upon moderate exertion, and attacks of tachycardia which he could stop by breathing deeply. Examination showed that he had tabes dorsalis, but no abnormality of the heart was detected. While he was under treatment, several attacks of tachycardia were observed; they were stopped by deep breathing. During normal rhythm there was marked sinus arrhythmia. Electrocardiograms showed that the tachycardia was of supraventricular origin. There was alternation of cycle length, as shown by the following measurements, in seconds: (Lead I) 0.383, 0.363, 0.387, 0.377, 0.399, 0.382, 0.397, 0.377, 0.397, 0.382, 0.388. (Lead III) 0.450, 0.453, 0.462, 0.456, 0.458, 0.442, 0.453, 0.450, 0.460, 0.456, 0.460.

In these cases the alternation in cycle length was apparent to the unaided eye. Measurements were made on the comparator only when inspection revealed the type of irregularity under consideration. It is possible that accurate measurements of other curves would disclose additional examples in which the alternation was less pronounced. Measurements in twenty unselected cases, eight reported by Feil and Gilder,[1] and twelve by Mackinnon,[5] disclosed this phenomenon in only two (Feil and Gilder). In one of these and in the case reported by Strong and Levine,[3] the variations in cycle length were so slight that they could scarcely be detected without accurate measurements. In none of our cases was the alternation of cycle length detected on physical examination.

In none of our cases, with the single exception of Case 7, and in none of those found in the literature, was the alternation of cycle length accompanied by any perceptible alternation or variation in the form or amplitude of the auricular deflections. Alternation in the form or amplitude of the ventricular deflections was somewhat more common.

DISCUSSION

It is possible to account for alternation of the cycle length in auricular paroxysmal tachycardia in a variety of different ways, but in the last analysis it must depend either upon (1) alternation of the interval elapsing between the liberation of successive impulses, or upon (2) alternation in the path or rate of impulse conduction. As to the first possibility, little can be said. The mechanism by which normal cardiac impulses are elaborated is not well understood, and it seems possible, if not probable, that in paroxysmal tachycardia impulses are formed abruptly by an entirely different process. Nevertheless, we know of no

published examples of alternation in cycle length which have been clearly shown to depend solely upon the discharge of impulses by a single center. Cases of bigeminy in which the paired beats are of normal outline, and identical, or nearly so, as regards the form of their component deflections, are not rare, but in such cases it seems probable that successive impulses are not alike in origin. They may be formed either by different centers or by different processes.

We are, on the other hand, familiar with forms of alternation dependent upon variations in the refractory period, absolute or relative, which force successive impulses to pursue different paths or modify the time of their conduction along the same path. Cases in which normal conduction through one of the main bundle branches alternates with block in the same branch, i. e., so-called partial bundle branch block, may be cited as an example of this phenomenon. If auricular paroxysmal tachycardia is caused by the activity of a parasystolic center, surrounded by a zone in which conductivity is depressed, alternation of the cycle length in this disorder may well be the result of a mechanism of the same kind. We may assume in this case that successive impulses pass from the parasystolic center to the main body of the auricular muscle by different routes, or that they travel the same route but require different times.

There is, however, what appears to us a more attractive hypothesis. Alternation of the auricular cycle length was observed by one of us[7] in a case of auricular flutter in which the auricular rate was 368 (cycle length about 0.163 second). The cycle length shortened, and alternation appeared, when the vagus was strongly stimulated by pressure upon the eye balls. The alternation was accompanied by a slight variation in the form of the circus deflections in the electrocardiogram. It was suggested that both of these phenomena were dependent on the same cause, namely, the presence in the main path of the circus wave of muscle which could not recover completely in the interval between successive circuits of the impulse. The circulating excitation wave was consequently forced to alternate between the shorter circular path in which this muscle lay and a slightly longer path which passed around it. A similar explanation may be offered for the occurrence of alternation in cycle length in auricular paroxysmal tachycardia if we assume that this disorder also is caused by circus rhythm. Uniformity in the contour of the auricular deflections when the length of the auricular cycle alternates requires that the longer and shorter paths be close together throughout their courses, or, at least, in that part which lies in auricular muscle which makes a major contribution to the P deflection. The variation in cycle length, however, is often considerable; it is frequently 0.05 second, and sometimes nearly 0.10 second. This suggests that the two paths must differ considerably in length. The absence of alternation in the form of the auricular deflections when

the alternation of cycle length is pronounced may be accounted for if we suppose that, as has been suggested previously,[8, 9] auricular paroxysmal tachycardia is caused by circus rhythm which involves either the sinoauricular or the atrioventricular node. There is evidence that the tissues of both of these nodes have a relatively long refractory period, and that conduction, in the latter at least, is comparatively slow. Thus a relatively slight alteration in the length of the path through one of the nodes could cause a considerable change in the duration of the cycle without modifying the form of the auricular deflection.

The occasional disturbance of the regular alternation of cycle length is explained by a slight change in the refractory period at times, permitting or causing the circus wave to take a slightly shorter or longer course, as the case may be. In the exceptional case in which there was alternation in the form of the auricular deflection, we may assume that the course of the circus wave was altered in the auricular muscle rather than in the node.

In a separate communication[9] it was pointed out that many of the features of auricular paroxysmal tachycardia can be explained by circus rhythm involving one of the nodes. Other features of auricular paroxysmal tachycardia have not yet been explained on this basis. Our observations on alternation of the cycle length in this condition were made with the purpose of collecting further evidence bearing on this problem. Although they may be explained in various ways, they seem to us consistent with, and to that extent to support, the view that auricular paroxysmal tachycardia is caused by circus rhythm involving one of the specialized auricular nodes. It is our intention to summarize in a subsequent communication the available evidence bearing on the mechanism of this disorder.

SUMMARY

1. Close inspection of the electrocardiograms in one hundred unselected cases of auricular paroxysmal tachycardia revealed ten cases in which there was a slight irregularity characterized by alternation in the lengths of the cycles.

2. This phenomenon may be explained in various ways, depending upon one's views as to the nature of the underlying mechanism in this disorder.

3. Our observations are consistent with, and to that extent support, the view that auricular paroxysmal tachycardia is caused by circus rhythm involving one of the specialized auricular nodes.

REFERENCES

1. Feil, H. S., and Gilder, M. D.: The Regularity of Simple Paroxysmal Tachycardia, Heart **8**: 1, 1921.
2. White, P. D.: Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, Arch. Int. Med. **25**: 420, 1920.

3. Strong, G. F., and Levine, S. A.: The Irregularity of the Ventricular Rate in Paroxysmal Ventricular Tachycardia, Heart **10**: 125, 1923.
4. Katz, L. N.: Electrocardiography, Philadelphia, 1941, Lea and Febiger.
5. Mackinnon, A. V.: The Rhythm of Paroxysmal Tachycardia. An Electrocardiographic Study, Quart. J. Med. **27**: 1, 1934.
6. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1925, Shaw and Sons, Ltd.
7. Wilson, F. N.: Report of a Case of Auricular Flutter in Which Vagus Stimulation Was Followed by an Increase in the Rate of the Circus Rhythm, Heart **11**: 61, 1924.
8. Ashman, R., and Hull, E.: Essentials of Electrocardiography, ed. 2, New York, 1941, The Macmillan Co.
9. Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W.: Auricular Paroxysmal Tachycardia With Auriculoventricular Block, AM. HEART J. **25**: 765, 1943.

CAPILLARY BLOOD PRESSURE IN MAN. DIRECT MEASUREMENTS IN THE DIGITS OF PATIENTS WITH RAYNAUD'S DISEASE AND SCLERODERMA BEFORE AND AFTER SYMPATHECTOMY

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BY MEANS of the direct microinjection method, Landis[1] measured the capillary blood pressure in the digits of three patients with Raynaud's disease during typical spastic and subsequent hyperemic stages. Previous studies[2, 3, 4] with the direct method demonstrated that a variety of factors induced changes in the digital capillary blood pressure which were qualitatively similar in both normal capillaries and the abnormally large capillaries of Raynaud's disease and scleroderma. These factors were neurogenic vasoconstrictor stimuli, epinephrine intravenously, reactive hyperemia, and elevation of arterial pressure produced by paredrinol sulfate.

The present communication reports additional observations on the digital capillary blood pressure of patients with Raynaud's disease and scleroderma both before and after interruption of the sympathetic innervation to the digits.

METHODS

General.—The capillary blood pressure was measured in the nail folds of the fingers by the direct microinjection method.[7, 8] The general methods, conditions, and precautions were similar to those described in detail in a previous communication under the category, *general.*[2] Except for measurements which were made during vasospastic circulatory arrest, capillary blood pressure was measured *only* when the blood flow in the capillary remained visibly unaltered from the normal.

Particular.—Of the eleven patients who were studied, seven were women and four were men. Nine of the patients had Raynaud's disease. In six of these there were associated sclerodermatous changes in the fingers. The other two patients had scleroderma alone. The arterial pressure was normal in eight of the patients, below 100 mm. Hg, systolic, in two, and above normal during the first measurement on the remaining subject.

The ready occurrence of vascular spasm, with circulatory arrest in the digits, almost always necessitated warming the body in order to obtain "moderate digital vasodilatation" (digital skin temperature between 30° C. and 33° C.). Such temperatures were not invariably attained, and comparable states of digital circulation from patient to patient could not always be obtained. Circulatory arrest in the nail folds was induced by exposing the fingers to room temperatures below 20° C. (usually 15° C. to 17° C.) and omitting the heating of the body. Local increases of venous pressure in the digits were produced by inflating a pneumatic cuff encircling the upper arm to pressures below diastolic arterial pressure.[8]

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Interruption of the sympathetic innervation to the digits was accomplished (1) temporarily, by injecting a 2 per cent procaine solution into the region of the stellate and upper thoracic sympathetic ganglia, and (2) permanently, by preganglionic sympathectomy. Preganglionic sympathectomy of the upper extremity, according to the method of Smithwick,[9] was achieved in three patients (F. G., C. M., and B. B.).

Capillary blood pressures represented by a single value indicate the average pressure in one capillary, and were obtained by averaging the individual values of a series of readings made during a single continuous observation on that capillary.

RESULTS

Not infrequently there was flushing of the nail folds in which capillary blood pressure was being measured, while the remainder of that finger and the other fingers remained grayish or purplish blue. This erythema was attributed to a disturbance of the local circulation in the minute vessels, caused, perhaps, by local liberation of H substance by the trauma of piercing the nail fold with the micropipette.

DIGITAL INNERVATION INTACT

Capillary Blood Pressure During Vasospastic Circulatory Arrest in the Digits.—During vasospastic circulatory arrest induced in the fingers by cold, the capillaries of the nail fold lost their pink color and smooth outlines. They became widely dilated loops of indented, irregular contour, filled with a stationary mass of dark, bluish-red blood. Apparently because of the loss of its fluid element, the blood became more compact and more viscid. This was indicated by the less free movement of erythrocytes into and out of the tip of the micropipette, by the frequent need of negative pressure to draw blood into the micropipette, and by the adherence of clumps of erythrocytes to the micropipette when it was withdrawn from the capillary.

In order to obtain accurate measurements, the compact mass of erythrocytes was first broken into a loose, freely moving suspension. This was accomplished by injecting a small amount of solution from the micropipette into the capillary. Fluid thus introduced was seen to drain quickly through the venous limb of the capillary and carry with it some of the compact erythrocyte mass, leaving behind a more loose suspension.

During vasospastic circulatory arrest, the digital capillary blood pressure in all portions of nine capillaries of three subjects varied between 7.0 mm. Hg and 12.5 mm. Hg (average, 9.7 mm. Hg) (Table I, Fig. 3 open circles).

When the digital circulation was normal, raising the venous pressure in the upper extremity caused the capillary blood pressure to rise promptly, and, within one to two minutes, to exceed the venous pressure.[8] During vasospastic circulatory arrest, a similar increase in the venous pressure induced a much slower rise in the capillary blood pressure. Five to seven minutes were required to attain maximum values. These

TABLE I

CAPILLARY BLOOD PRESSURE DURING CIRCULATORY ARREST INDUCED BY COLD, AND DURING SUBSEQUENT REFLEX VASODILATATION

SUBJECT, SEX, AGE	CHARACTER OF CAPILLARY LOOPS	LOCATION IN CAPILLARY WHERE BLOOD PRESSURE WAS MEASURED	CIRCULATORY ARREST				REFLEX VASODILATATION			
			SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. HG		CAPILLARY BLOOD PRESSURE MM. HG	SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. HG		CAPILLARY BLOOD PRESSURE MM. HG
				READING	"MEAN"			READING	"MEAN"	
A. L. (M, 27)	Large dilated	Summit	14.9	104/64	84	11				
		Summit	14.9	104/64	84	12.5				
		Summit	14.9	104/64	84	16*	22.2	104/74	89	40
M. L. (F, 48)	Large dilated	{Summit	14.6	110/72	91	11.5				
		{Venous limb	14.6	110/72	91	7				
F. G. (M, 31)	Large dilated	Venous limb	16.2	104/66	85	8				
		Venous limb	14.6	122/74	98	8.5	20.5	122/74	98	24
		Venous limb	20.9?	122/74	98	11	20.3	122/74	98	23.5 to 34.5
		{Venous limb	16.2	104/66	85	9.5				
		{Arteriolar limb	16.2	104/66	85	11.5				
		Arteriolar limb	14.6	122/74	98	9				
		Summit	16.4	104/66	85	7.5				

*Very slow flow through capillary persisted.
Two sets of observations made on a single capillary are indicated by brackets.

approximated, but failed by 2 to 3 mm. Hg to equal, the increased venous pressure (Fig. 1). Suddenly lowering the elevated venous pressure to its initial level caused the capillary blood pressure to fall quickly to its original level (Fig. 1). The rapidity of this fall equalled that which occurred when the capillary blood flow was swiftly onward.

Releasing digital vasospasm by producing reflex vasodilatation caused the blood flow to return in the capillaries, and digital capillary blood pressure to increase at times to values above those usually encountered. In three capillaries, maximum values of 24, 34.5, and 40 mm. Hg were obtained (Table I). The digital skin temperature lagged considerably behind the return of capillary blood flow and the rise in capillary blood pressure (Table I).

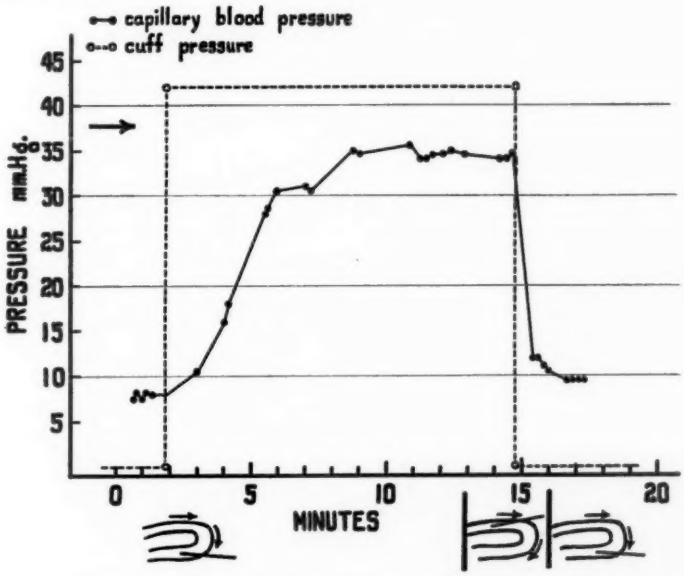

Fig. 1.—Response of the blood pressure in a single digital capillary to increased venous pressure during vasospastic circulatory arrest induced by cold.
The ordinates indicate pressure (mm. Hg) in both the occluding cuff and the capillary; the abscissae, time in minutes. The solid line indicates capillary blood pressure, and the dotted line, pressure in the occluding cuff. The large horizontal arrow indicates venous pressure in the back of the hand when the cuff pressure was 42 mm. Hg. In the diagrams of the capillary, the straight line shows the location of the micropipette in the capillary, and the arrows, the direction of blood flow before circulatory arrest.

When the circulation returned to the capillaries after a period of vasospastic circulatory arrest, stationary erythrocytes were found just beyond the visible summits of a few capillaries. These erythrocytes were not in the visible current of the capillary blood stream, and appeared to be not even connected with the adjacent capillaries. Such erythrocytes were present in either of two forms: (a) as loose aggregations of widely-spaced, stationary, individual cells ("fuzz") (Fig. 2*A*), and (b) as small, compact, nonmoving masses of packed cells ("buttons") (Fig. 2*B*). There is reason to believe that these aggregations

of erythrocytes are not extracapillary, as they appear to be, but are actually intracapillary.

On one occasion, individual erythrocytes were repeatedly thrown off from the visible capillary stream at the junction of the arteriolar limb with the summit. Flung beyond the visible summit, these cells became stationary, and, when joined by others, formed a loose aggregation ("fuzz"). In time, closer clumping occurred, but no compact mass ("button") was formed. Occasionally, a few well-separated, stationary erythrocytes connected a compact clump ("button") with the visible summit of the capillary (Fig. 2*C*).

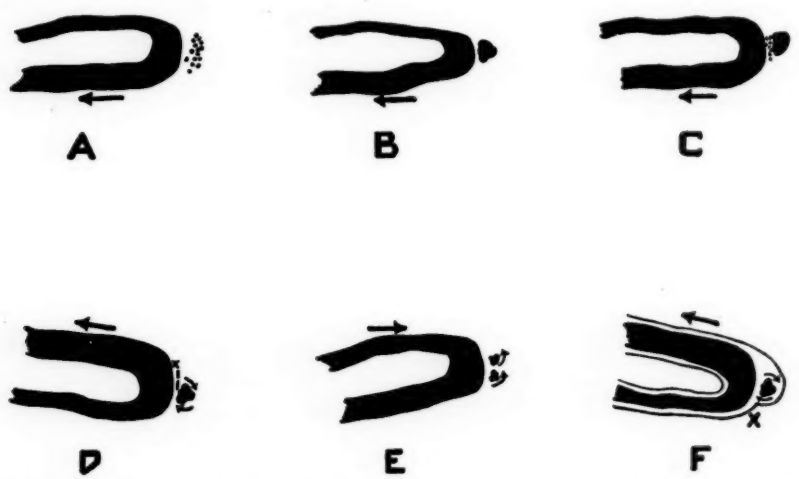

Fig. 2.—Diagram of types of erythrocyte aggregation found outside the visible summit of the capillary when digital circulation returned after a period of standstill.

The capillary is diagramed in black; the large arrows indicate the direction of blood flow, and the small arrows, the direction of rotation of clumps of erythrocytes.

A, Loose aggregation of individual erythrocytes ("fuzz"); *B*, single, stationary clump of packed erythrocytes ("button"); *C*, individual cells connecting summit of capillary blood stream with a clump of packed cells; *D*, single clump of packed erythrocytes in rotation ("pinwheel"). The dotted arrow indicates the path followed by the clump in returning to the main stream; *E*, two separate clumps of erythrocytes rotating beyond the summit of a single capillary; *F*, possible mechanism by which erythrocytes remain outside the main capillary stream.

Peripheral to the erythrocyte portion of the capillary blood stream is the clear plasma layer. It is assumed that, at the junction of the arteriolar limb with the summit (point X) there is a localized capillary constriction which deflects the blood flow from the summit.

On several occasions, compact masses of erythrocytes were rotating like "pinwheels" just beyond the visible summit of the capillary (Fig. 2*D*). These masses were usually of irregular contour, and their rotation always took place in a direction opposite that of the current in the adjacent capillary. Two separate clumps have been found rotating beyond the summit of a single capillary (Fig. 2*E*). Once a rotating clump of erythrocytes was observed to move slowly toward the venous limb of the capillary, and then suddenly enter the main capillary stream at the junction of the venous limb with the summit (Fig. 2*D*, dotted arrow). In a similar manner, loose aggregations of erythrocytes ("fuzz") have been seen to enter the adjacent capillary.

Capillary Blood Pressure When Digital Blood Flow Was "Normal." —The capillary blood pressure in the same location of the same capillary was quite constant (variation, 2 to 3 mm. Hg) throughout any single experiment when the digital skin temperature remained relatively unchanged (Table II), but from person to person, and even from capillary to capillary in the same subject, the capillary blood pressure varied considerably, even though the digital skin temperature was brought to the same level (Fig. 3). These variations were usually less marked than those previously observed in normal and hypertensive subjects.[3]

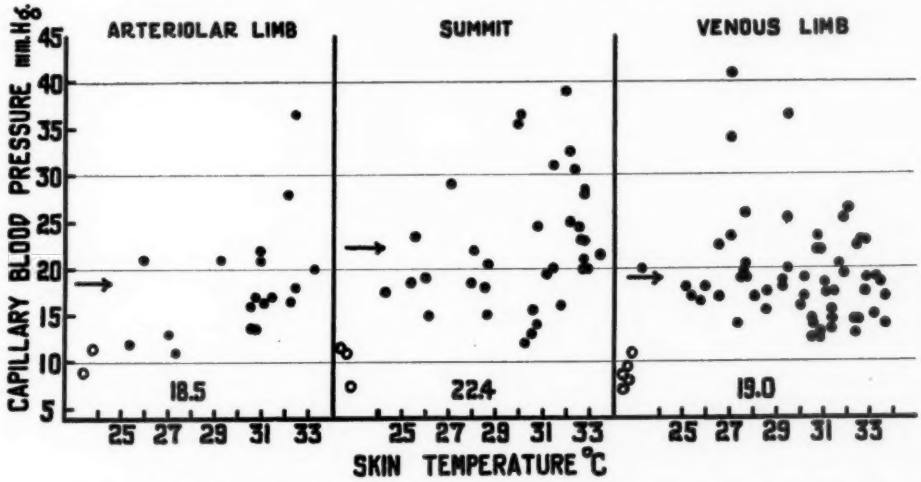

Fig. 3.—Digital capillary blood pressure in different locations in the capillary at varying digital skin temperatures. Digital innervation intact.

Pressures, represented by open circles, were obtained during vasospastic circulatory arrest (skin temperatures about 15° C.) and all others during active blood flow.

Figs. 3, 4, 5 are similarly constructed. Ordinates, digital capillary blood pressure in mm. Hg; abscissae, digital skin temperature in degrees Centigrade. Each dot represents the average capillary blood pressure in the designated location of a single capillary at the skin temperature indicated by the abscissa. Each horizontal arrow and number above the abscissa line gives the average of the pressures represented by the corresponding dots.

Skin Temperature.—No measurements of digital capillary blood pressure in the same capillary during large changes in digital skin temperature were obtained. However, the skin temperature was measured at the time of each measurement of capillary blood pressure. This permits evaluation of the relationship between the two (Fig. 3). Over a wide range of temperatures (from 24° C. to 33.5° C.), the digital capillary blood pressure did not change significantly with the skin temperature (Fig. 3). Excluding values obtained during circulatory arrest, the capillary blood pressure and its range of variation were similar at all levels of skin temperature. Only in the summit of the capillary at the higher temperatures (31° C. to 33° C.) was there a tendency toward higher values. This was regarded as inconclusive.

Gradient of Fall of Pressure Through the Capillary.—The average digital capillary blood pressure in eighteen arteriolar limbs was 18.5 mm.

TABLE II

SUCCESSIVE MEASUREMENTS OF CAPILLARY BLOOD PRESSURE IN THE SAME LOCATION IN A SINGLE CAPILLARY DURING ONE OBSERVATION PERIOD

SUBJECT, SEX, AGE	CHARACTER OF CAPILLARY LOOPS	LOCATION IN CAPILLARY WHERE BLOOD PRESSURE WAS MEASURED	FIRST MEASUREMENT				SECOND MEASUREMENT				DIFFERENCE MM. HG
			SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. HG		CAPILLARY BLOOD PRESSURE MM. HG	SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. HG		CAPILLARY BLOOD PRESSURE MM. HG	
				READING	"MEAN"			READING	"MEAN"		
A. Innervation Intact											
T. A. (M, 26)	Large dilated	Arteriolar limb	30.9	90/56	73	21	30.9	96/56	76	22	1.0
F. H. (M, 38)	Moderately large	Venous limb	30.7	118/62	90	22	30.7	118/62	90	22	0.0
M. S. (F, 19)	Large dilated	Venous limb	29.2	86/50	68	18	30.0	94/60	77	16	2.0
C. M. (F, 29)	Large dilated	Venous limb	27.0	128/86	107	34	27.0	128/86	107	41	7.0
		Summit	27.0	128/86	107	29	26.1	128/86	107	15	14
		Summit	32.7	120/78	99	28	32.3	120/78	99	30.5	2.5
F. G. (M, 31)	Large dilated	Summit	33.4	118/78	98	21.5	32.7	124/84	104	23	1.5
		Venous limb	33.4	118/78	98	18.5	32.3	125/86	106	19.5	1.0
		Venous limb	30.1	130/82	106	19	27.5	116/78	97	19	0.0
		Venous limb	29.2	130/82	106	18.5	27.5	116/78	97	19.5	1.0
M. L. (F, 48)	Large dilated	Venous limb	29.0	?		24	31.0	108/62	85	21	3.0
B. B. (F, 44)	Quite normal	Summit	25.3	110/76	93	18.5	27.9	122/86	104	18.5	0.0
B. Sympathetic Innervation Interrupted											
B. B. (F, 44)	Quite normal	Summit	29.4	106/76	91	19.5	29.4	106/76	91	17	2.5
F. G. (M, 31)	Large dilated	Summit	31.9	110/80	95	18.0	34.0	110/80	95	17.5	0.5
		Venous limb	32.8	116/76	96	17.5	31.2	128/88	108	23	5.5
C. M. (F, 29)	Large dilated	Venous limb	32.4	126/86	106	29.5	33.8	122/82	102	26	3.5

Hg (range, 11 to 36.5 mm. Hg); in thirty-one summits, 22.4 mm. Hg (range, 12 to 39 mm. Hg); and in fifty-two venous limbs, 19 mm. Hg (range, 12.5 to 41 mm. Hg) (Fig. 3). Hence, the gradient of fall of pressure in these dilated capillaries was small, namely, 2 to 3 mm. Hg.

Even more significant was the absence of a gradient of more than a few millimeters of mercury between the various locations of the *same* capillary when measurements were made in a single experiment during which digital skin temperature and brachial arterial pressure remained constant (Table III).

It is emphasized that the majority of these measurements, both in the same and in different capillaries, were made when there was "moderate vasodilatation" (skin temperature, 30°+ C.), and blood flowed swiftly and continuously onward through the capillaries.

SYMPATHETIC INNERVATION OF THE DIGITS INTERRUPTED

In some cases, preganglionic sympathectomy of the upper extremity was followed by a return toward normal in the morphology of the capillaries. The abnormally large loops, with slowly flowing, bluish-red blood, became smaller, narrower loops containing rapidly flowing, pink blood. This change was attributed, not to the removal of the sympathetic innervation per se, but to the improvement in digital circulation which followed the abolition of periods of circulatory arrest. A similar change was noted in one case after one month's hospitalization in a warm environment. During this period, vasospastic periods spontaneously became much less frequent and less prolonged.

Even after removal of sympathetic activity by satisfactory preganglionic sympathectomy, the digital capillary blood pressure still varied considerably from subject to subject (Fig. 4), and even from capillary to capillary in the same subject during a single experiment.

Skin Temperature.—After sympathectomy, the digital skin temperatures were higher, ranging between 30° C. and 35° C. At all skin temperatures throughout this range, the capillary blood pressures for all locations in the capillary fell within the same limits. There was no relationship between capillary pressure and digital skin temperature (Fig. 4).

When the digital skin temperature remained relatively constant (variation less than 2° C.), repeated measurements of the capillary blood pressure in the same location of the same capillary varied but slightly (5.5 mm. Hg) (Table II).

Gradient of Fall of Pressure Through the Capillary.—The average digital capillary blood pressure in eleven arteriolar limbs was 27.8 mm. Hg (range, 19.5 to 36 mm. Hg); in twenty-four summits, 25.2 mm. Hg (range, 14 to 40 mm. Hg); and in twenty-four venous limbs, 21.6

TABLE III

CAPILLARY BLOOD PRESSURE IN DIFFERENT LOCATIONS IN THE SAME CAPILLARY. DIGITAL SKIN TEMPERATURE AND BRACHIAL ARTERIAL PRESSURE CONSTANT

SUBJECT, SEX, AGE	CHARACTER OF CAPILLARY LOOP	SKIN TEMP. ° C.	ARTERIAL PRESSURE MM. HG		CAPILLARY BLOOD PRESSURE MM. HG				GRADIENT
			READING	"MEAN"	ARTERIOLAR LIMB	SUMMIT	VENOUS LIMB	VENULE	
A. Innervation Intact									
F. H. (M, 38)	Moderately large	30.7	118/62	90		24.5	22		+2.5
B. B. (F, 44)	Quite normal	25.3	110/76	93		18.5	17		+1.5
T. A. (M, 26)	Large dilated	30.9	96/56	76	22			15	+7.0
	Large dilated	31.1	90/56	73	16.5		17.5		−1.0
F. G. (M, 31)	Large dilated	30.7	126/80	103	17		23.5		−6.5
		32.7	124/84	104		20	23		−3
		32.7	116/80	98		23	17.5		+5.5
		30.5	104/66	85	13.5	13	12.5		+0.5, +0.5
		30.5	104/66	85	16	15.5	14.5		+0.5, +1.0
E. B. (F, 44)	Large and normal	25.9	170/116	143	21	19	18		+2, +1
B. Sympathetic Innervation Interrupted									
C. M. (F, 29)	Large dilated	30.7	114/82	98	36	27			+9.0
F. G. (M, 31)	Large dilated	31.9	110/80	95	27	18			+9.0
		31.4	122/86	104	26		32.5		−6.5
B. B. (F, 44)	Quite normal	30.5	106/78	92	32.5		16		+16.5
		30.4	110/76	91	21	20			+1.0
		30.3	110/76	93	34	36			−2.0
		29.4	106/76	91		19.5	13.5		+6.0
F. H. (M, 38)	Moderately large	29.0	122/70	96		35.5	32.5		+3.0

mm. Hg (range, 13.5 to 40 mm. Hg). The gradient of fall of pressure through these capillaries was, therefore, relatively small, and more apparent in the average values than in the scatter chart of all measurements (Fig. 4). A moderate gradient through the capillary was present when the digital capillary blood pressure was measured in different locations of the same capillary during a single experiment throughout which skin temperature remained constant (Table III).

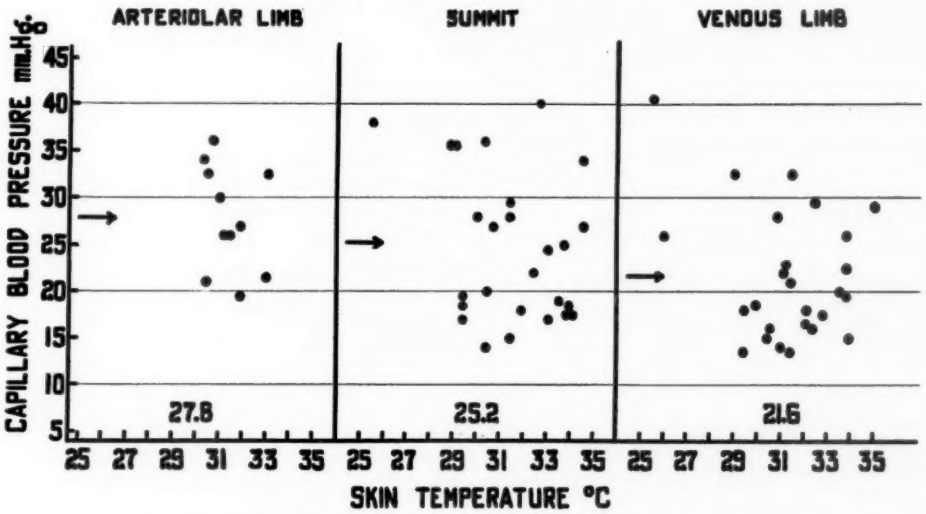

Fig. 4.—Digital capillary blood pressure in different locations in the capillary at varying digital skin temperatures. Sympathetic innervation interrupted.
Gradient of fall of pressure through the capillary is greater than during intact innervation, but is still small.

COMPARISON OF CAPILLARY BLOOD PRESSURE WHEN THE INNERVATION WAS INTACT WITH THAT AFTER INTERRUPTION OF SYMPATHETIC ACTIVITY

Although the average capillary blood pressure for each location in the capillary was somewhat higher after interruption of sympathetic activity than before interruption (Fig. 5), this was striking for only the pressures in the arteriolar limb. In this location the average pressure was 9.3 mm. Hg higher after sympathectomy than before, and the individual values scattered over a higher range. In the summit and venous limb the individual values scattered over the same limits after sympathectomy as before, and the differences in the average values were but 2.8 mm. Hg for the summit and 2.6 mm. Hg for the venous limb. The gradient of fall of pressure in the capillary seemed more definite after interruption of sympathetic activity than before (Table III, Fig. 4).

In only one case was the capillary blood pressure measured in the same location of the same capillary (two venous limbs) both before and after sympathectomy. In one venous limb the pressure before sympathectomy was 15 to 19 mm. Hg, and after sympathectomy, 19.5 mm. Hg; in the

other venous limb, before sympathectomy, it was 13.5 to 18.5 mm. Hg, and, after sympathectomy, 22.5 mm. Hg.

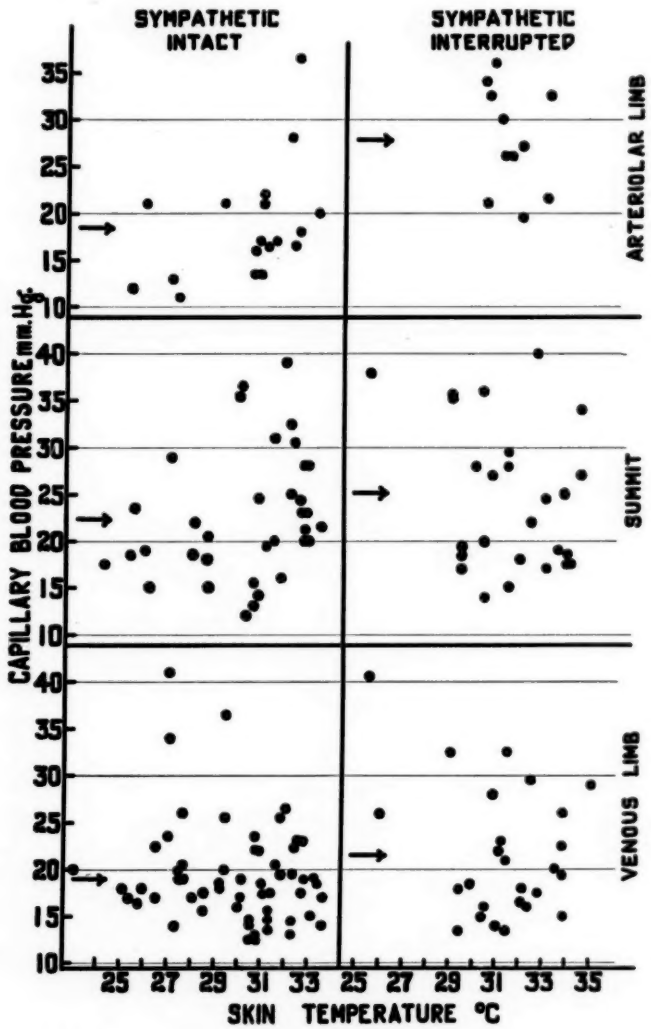

Fig. 5.—Digital capillary blood pressure in different locations in the capillary when innervation was intact, compared with similar pressures obtained after interruption of sympathetic innervation.

DISCUSSION

The digital capillary blood pressures of 7.0 to 12.5 mm. Hg during vasospastic circulatory arrest and 24 to 40 mm. Hg during subsequently induced reflex vasodilatation agree favorably with the values obtained by Landis[1] under similar conditions. Our data also confirm the observations and conclusions of Landis[1] that vasospastic circulatory arrest in the digits is precapillary in origin, and that it is associated with patency

of the capillaries and venous channels. The following observations, made during circulatory arrest in the capillary, substantiate this conclusion: (1) When fluid is injected into the capillary it drains readily out of the venous limb; (2) capillary blood pressure rises slowly during an induced increase in venous pressure in the upper extremity; and (3) capillary blood pressure falls promptly when the increased venous pressure is quickly reduced.

Several factors may explain why erythrocytes are found beyond the visible capillary blood stream when digital circulation returns after a period of arrest: (1) The assumption that capillaries possess independent, localized contractility,[10] and (2) the fact that blood flows through the capillary in an axial stream, the central erythrocyte portion of which is visible, and the peripheral plasma layer, invisible.

Localized constriction of the capillary at the junction of the arteriolar limb with the summit (point *x*, Fig. 2*F*) would produce an indentation at this point. This protrusion would deflect the blood stream and prevent it from sweeping into the outermost summit of the capillary, where now a stagnant "pool" is formed. Such a localized constriction during vasospastic circulatory arrest, if it persisted after the return of blood flow in the capillary, could trap a compact clump of cells ("button") in the "pool" at the summit. The clear plasma layer between the clump of cells and the visible erythrocyte portion of the axial stream gives the illusion that the clump is outside the capillary. When the plasma layer of the capillary stream impinges on the excrescences of the clump of cells, the entire mass is set into rotation like a "pinwheel"; otherwise, the mass remains stationary. As the capillary stream sweeps past the indentation, it may fling off individual erythrocytes into the "pool" at the summit, where they accumulate in loose aggregations ("fuzz"). Relaxation of the local constriction would permit the capillary stream to sweep into the "pool" at the summit and carry away in itself everything therein contained.

The anoxemia of circulatory arrest may so damage the capillary endothelium that it becomes sticky, causing erythrocytes to adhere to it. This may also be a factor in holding stationary individual or clumped erythrocytes against the force of the peripheral layer of the capillary blood stream.

A widely accepted view holds that the gradient of pressure from the arteriolar to the venous limb of the capillary is of considerable magnitude (20 mm. Hg). It is, therefore, significant that in the abnormally large capillaries of these patients the gradient of pressure between the arteriolar and venous limbs was small (2 to 3 mm. Hg). This was maintained even during the swift blood flow associated with "moderate digital vasodilatation." In these capillaries a small gradient of pressure is sufficient to produce a swift flow of blood, and factors other than capillary blood pressure and blood osmotic pressure influence the passage of fluid through the capillary membrane.

In abnormally large capillaries, just as in those of normal size, wide variations in digital skin temperature (24° C. to 34° C.) were not accompanied by significant changes in digital capillary blood pressure. Only when the digital circulation slowed markedly, or stopped completely, did the capillary blood pressure fall outside the usual range. In these abnormally large capillaries there also appears to be a homeostatic mechanism[3] which permits wide fluctuations in digital blood flow without great change in digital capillary blood pressure.

When compared at similar digital skin temperatures, the capillary blood pressure after loss of sympathetic activity was not strikingly different from that before sympathectomy (Fig. 5). In the summits and venous limbs no significant differences were evident. The somewhat greater capillary blood pressures in the arteriolar limb after sympathectomy suggest a release, at least to some extent, of arteriolar tonus.

SUMMARY

1. During vasospastic circulatory arrest, induced in the fingers by cold, (a) digital capillary blood pressure varied between 7.0 and 12.5 mm. Hg (average, 9.7 mm. Hg); (b) digital capillary blood pressure *rose slowly* in response to induced increases in venous pressure, but *fell promptly* when the increased venous pressure was suddenly lowered; (c) cessation of blood flow through the capillaries was caused by closure of vessels proximal to them. The capillaries, venules, and veins remained patent.

2. Erythrocytes in clumps or loose aggregations may be isolated outside the central capillary blood stream when the digital circulation returns after a period of vasospastic circulatory arrest. Localized constriction of the capillary, or stickiness of the capillary endothelium, or both, may account for this.

3. In fingers with intact innervation the average digital capillary blood pressure was as follows: arteriolar limb, 18.5 mm. Hg; summit, 22.4 mm. Hg; and venous limb, 19 mm. Hg. The gradient of fall of pressure through the capillary was small, usually less than 3 mm. Hg.

4. In fingers deprived of sympathetic innervation the average digital capillary blood pressure was as follows: arteriolar limb, 27.8 mm. Hg; summit, 25.2 mm. Hg; and venous limb, 21.6 mm. Hg. The somewhat greater capillary pressure in the arteriolar limb suggests release of arteriolar tone. The gradient of pressure in the capillary is still small (6 to 7 mm. Hg).

The author wishes to thank Dr. James Bordley, III, for constant and helpful advice and criticism throughout the study; Dr. Harris B. Shumacker, Jr., for interrupting the sympathetic activity to the upper extremity, both by the injection of procaine and by operation; and Mr. William A. Oktavec, Jr., and Miss Margot Robinson for technical assistance.

REFERENCES

1. Landis, E. M.: Micro-injection Studies of Capillary Blood Pressure in Raynaud's Disease, Heart **15**: 247, 1930.
2. Eichna, L. W., and Wilkins, R. W.: Capillary Blood Pressure in Man. Direct Measurements in the Digits During Induced Vasoconstriction, J. Clin. Investigation **21**: 697, 1942.
3. Eichna, L. W., and Bordley, J., III: Capillary Blood Pressure in Man. Direct Measurements in the Digits of Normal and Hypertensive Subjects During Vasoconstriction and Vasodilatation Variously Induced, J. Clin. Investigation **21**: 711, 1942.
4. Eichna, L. W.: Capillary Blood Pressure in Man. Direct Measurements in the Digits During Arterial Hypertension Induced by Paredrinol Sulfate, J. Clin. Investigation **21**: 731, 1942.
5. Brown, G. E.: The Skin Capillaries in Raynaud's Disease, Arch. Int. Med. **35**: 56, 1925.
6. Brown, G. E., and O'Leary, P. A.: Skin Capillaries in Scleroderma, Arch. Int. Med. **36**: 73, 1925.
7. Landis, E. M.: Micro-injection Studies of Capillary Blood Pressure in Human Skin, Heart **15**: 209, 1930.
8. Eichna, L. W., and Bordley, J., III: Capillary Blood Pressure in Man. Comparison of Direct and Indirect Methods of Measurement, J. Clin. Investigation **18**: 695, 1939.
9. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity. A Preliminary Report, Ann. Surg. **104**: 339, 1936.
10. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, 1929. Yale University Press, Chapter 3.

Clinical Reports

ANEURYSM OF THE ABDOMINAL AORTA, WITH RUPTURE INTO THE DUODENUM

Case Report and Review of the Literature

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THE purpose of this paper is to present a case of abdominal aneurysm which ruptured into the duodenum, and to review thirty-one similar cases from the literature. Although the first of these was found in 1843,[2] the phenomenon must have been observed prior to that time, for Chamel and Dalmas,[1] in 1833, stated that "rupture into the gastrointestinal tract is one of the complications of abdominal aneurysm."

Table I gives the essential data in each of the thirty-one cases.[2-31] There were twenty-five males and five females (in one case the sex was not given). The patients' ages varied from 20 to 81 years. Between these extremes, the distribution of cases is fairly even.

The usual manifestations were abdominal pain, an abdominal mass, hematemesis, melena, and shock. The combination of these symptoms and their rapidity of development varied from case to case. Bernacchi's[10] patient had been cognizant of an enlarging abdominal mass for many years; during convalescence from pneumonia, after days of abdominal pain, he was awakened from sleep by hematemesis, which was followed rapidly by death. In a second case the patient was aware of an abdominal mass for two years before hematemesis occurred and death ensued. Other patients gave histories of gradually progressing weakness, with subsequent hemorrhages from the gastrointestinal tract. In still others, prodromal symptoms were present in the form of pain in the epigastrium, lumbar area, umbilical region, or in the loin. In some instances these symptoms were present as long as two years before the aneurysm ruptured. Particularly puzzling was a patient with symptoms of peptic ulcer for many years; suddenly, severe pains developed and hematemesis followed.

The time relationship of death to the onset of hematemesis varied. It was almost immediate in some cases, and, in others, was as long as six weeks. In the interim, one or many recurrences of melena and bloody vomiting occurred.

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The most important physical sign was a palpable abdominal mass, usually above the umbilicus and to the left of the midline. Pulsation was present, as a rule, but was rarely expansile in nature. In some cases a thrill was felt and a murmur heard.

Pathologic Observations.—Most of the aneurysms were of the saccular type; others were so-called aneurysmal dilatations. Their location in relation to the branches of the abdominal aorta was given in only a few instances. One aneurysm was close to the diaphragm, and the others were found at all levels from above the celiac axis to just above the bifurcation of the aorta. In regard to organs perforated by the aneurysms, five ruptured into the stomach,[9, 16, 23, 24, 27] one into the jejunum,[15] one into the small intestine[4] (the exact site was not specified), and twenty-four into the duodenum (twenty-three into the third part, one into the second part).

CASE REPORT

A white man, aged 53, entered St. Vincent's Hospital, New York City, Aug. 20, 1935, complaining of painful "arthritis" of the right hip. In May, 1935, he had had Type I pneumococcus pneumonia, complicated by empyema, and later by arthritis. On admission it was noted that the limb in question was shortened slightly, and was rigid because of pain. Roentgenologic study disclosed destruction of the articular cartilages and narrowing of the joint space. For the remaining three months of his life the patient was bedridden. During the first half of this period he seemed more or less comfortable, after which he began to complain of constant pain in the epigastrium. At first the only abnormality was tenderness and spasm of the rectus muscles. Later, a pulsating mass became palpable in the epigastric region. The mass increased in size until it reached that of a small orange. A bruit was heard over it. Two days before death the patient had sudden hematemesis; this recurred several times, and was followed by melena up to the time of death. The blood Kahn reaction was negative. Roentgenologic study of the stomach showed a deformity suggesting extrinsic pressure. The gastric contents and urine were normal. Throughout the course there was a fever of 99.6° F., with an occasional rise to 100° F. One blood cell count a month before death showed 12,400 leucocytes, 67 per cent polymorphonuclear leucocytes, 28 per cent lymphocytes, four monocytes, and one eosinophil.

Autopsy.—The important lesions were in the abdominal aorta and duodenum. On the anterior surface of the aorta, 2½ cm. below the renal arteries, there was a saccular aneurysm which measured 7½ × 7 × 4 cm. Its external surface was firmly adherent to the outer surface of the third portion of the duodenum. The adhesion was thick and fibrous, and could not be separated without tearing both structures. On opening the aorta it was found that the aneurysm was filled with a firm thrombus, and that it communicated with the lumen of the aorta through an opening 4 cm. in diameter (Fig. 1).

The rest of the aorta was not dilated and was elastic. Just above the aortic valves, and in the arch, small flecks of atheroma were observed. Scattered through the descending thoracic and abdominal portions were raised yellow plaques. No gross changes suggestive of syphilis were observed except around the upper rim of the aneurysm, where the intima was wrinkled, raised, and pearly grey.

On opening the gastrointestinal tract an irregular perforation was found in the posterior wall of the mid-transverse limb of the duodenum; this opening communicated with the underlying, adherent aneurysm (Fig. 2). A thin strand of

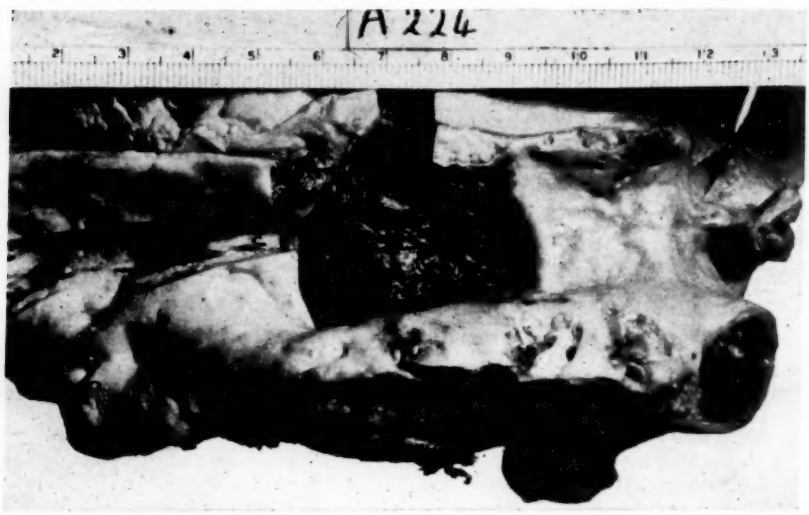

Fig. 1.—Abdominal aorta opened posteriorly, exposing mouth of aneurysm. Aneurysm itself is filled with thrombus. Defects at margins (*c*) are caused by removal of blocks of tissue. *a* indicates mouth of celiac axis. *b* indicates mouth of superior mesenteric artery.

Fig. 2.—Third portion of the duodenum. Note the irregular ulcer. A small band of mucosa extends from one margin to the other.

duodenal mucosa extended across the perforation. The margins of the perforated area were sharp, and showed nothing indicative of a pre-existing peptic ulcer. Clotted and free blood was found in the stomach and in the small and large intestine.

The heart weighted 350 Gm. and appeared to be well preserved.

Anatomic Diagnosis.—Saccular aneurysm of the anterior wall of the abdominal aorta, with rupture into the third portion of the duodenum; massive hemorrhage into the gastrointestinal tract; ischemia of the liver and kidney; mild atherosclerosis of the aorta; mild atherosclerosis of the cerebral vessels.

Microscopic Study of the Aorta.—All of the ascending aorta was cut into serial blocks in such a manner as to include its entire circumference. Many sections were prepared from the descending aorta, especially through the aneurysm. The stains employed were hematoxylin and eosin, Weigert's elastic tissue stain, the Masson-Goldner trichrome stain, and the Giemsa and Gram stain for bacteria.

Only minor changes were observed in the ascending aorta, such as atherosclerosis with focal compression atrophy of the underlying media, occasional zones of medial degeneration of the "muscle loss" type, and a sprinkling of fine granules of calcium. Nothing more significant was found elsewhere until sections through the aneurysm were studied. Since all of its layers exhibited alterations, it might be well to consider each tunic separately, and describe the changes as they were seen from just above to just below the sac.

The intima above, around, and below the aneurysm was densely fibrous. At the margins the same sclerotic thickening was observed, together with several atherosclerotic plaques. In the adjacent aneurysmal wall some of these were ulcerated and covered by thrombus.

The media presented a varying appearance. That immediately superior to the aneurysm contained endothelial-lined channels of wide caliber, lymphocytes, and large round cells. The changes did not resemble those of syphilis. As the media dipped into the aneurysmal sac it split and disappeared, so that in its depth only hyalinized fibrous tissue made up the wall.

The elastic media of the inferior wall of the aneurysm was compressed into a narrow layer devoid of muscle cells. Just below the sac the elastic lamellae were reduced in numbers and were thin and fragmented. The adventitia over the entire aneurysm was thick and fibrotic. Portions of adjoining structures, such as the duodenum and the inferior vena cava, were intimately fused with it. Incorporated in it was the inferior mesenteric artery, which was thick walled and thrombosed. The thrombus was completely organized. Scattered through the adventitia were numerous lymphocytes and large collections of macrophages filled with hemosiderin. In several fields there were dense collections of polymorphonuclear leucocytes, forming abscesses ½ mm. in diameter. In one of the abscesses there were many large, Gram-positive bacilli which resembled *B. subtilis* morphologically. The organisms were also seen on the lumen surface of the thrombus which filled the aneurysm. The thrombus itself, at its junction with the surface of the aorta, showed fibroblastic proliferation.

Section of other organs disclosed arteriosclerosis of the pulmonary vessels, anthracosis of the lung, mild granular degeneration of the liver cells, ischemia of the spleen, arteriosclerosis of the small renal arteries, and mild atrophy of the testicular tubules. The pancreas, thyroid, adrenal, pituitary, and parathyroid were apparently normal. Search for bacteria beyond the aneurysm was fruitless.

This case illustrates one of the rarer sites of rupture of abdominal aneurysms. The cause of the aneurysm can only be surmised. There seems to be no reason to implicate syphilis. The same applies to trauma and tuberculosis. However, atherosclerosis, a common cause of ab-

TABLE I

CLINICAL DATA

	DATE	AUTHOR	AGE	SEX	PERTINENT HISTORY LEADING TO ADMISSION	CLINICAL OBSERVATIONS	COURSE	PATHOLOGIC CHANGES
1	1843	Salmon[2]	59	M	Ill for about 1 month. Weakness and intestinal hemorrhage	Tender, hard mass felt. There was no murmur or thrill. Patient in shock	Died in 4 hours	Orange-sized, saccular aneurysm below superior mesenteric, adherent to third portion of duodenum, perforating latter
2	1859	Johnson[3]	37	M	Back pain 1 year. Epigastric swelling 7 weeks	Pulsating epigastric mass to left of midline. No murmurs present	Mass enlarged, murmur developed over it. He had sudden hematemesis and died rapidly	Gumma of liver, aneurysm anterior wall perforating third portion of duodenum and eroding vertebrae
3	1862	Seligman[4]	47	M	Colicky pain over kidney radiating down loin to testes, few days' duration	Firm, fixed mass felt about the navel	Died suddenly in bed, 6 months after onset of pain	Marked arteriosclerosis of abdominal aorta, with dilatation, adhesion to small bowel, and perforation
4	1874	Stich[5]	Aged	F	Sudden hematemesis		Recurrence of hematemesis. Died in 2 weeks	Severe arteriosclerosis of abdominal aorta, dilatation, ulceration of a plaque, with perforation through this into adherent, adjacent third portion duodenum
5	1878	Von Vehling[6]	74	F	Sudden collapse		Rapid death	Egg-sized saccular aneurysm fixed to and perforating third portion of duodenum. Severe arteriosclerosis present
6	1883	Coupland[7]	72	M	Weakness, loss of weight, about 3 months' duration. Sudden abdominal pain and collapse	Tender, pulsating, oval mass to right of midline. No bruit	Three months after first acute episode, had a second one associated with severe abdominal pain. Death sudden 5 days later	Saccular aneurysm, filled with thrombus, located below renal vessels, with perforation into third portion of duodenum. Marked arteriosclerosis present
7	1891	Dickenson[8]	28	M	History of syphilis. Epigastric pain 6 months, backache and loss of weight. Sudden collapse, tarry stools		Three days before death, became jaundiced. Death occurred suddenly after profuse hematemesis	Large saccular aneurysm lying above the celiac axis, compressing the common duct and rupturing into second part of duodenum

8	1891	Bailey[9]	45	M	Abdominal mass 2 years. Back pain 2 years. Sudden hematemesis and shock	Pulsating epigastric mass. Bruit present	Repeated hematemesis and death after 8 days	Large aneurysm perforating into stomach
9	1892	Bernacchi[10]	52	M	Abdominal mass many years. Pain about umbilicus, few days	Slightly tender pulsating mass felt in epigastrium	Awoke from sleep vomiting blood. Died after 8 days	Apple-sized aneurysm adherent to, and perforating, third portion of duodenum. Many arteriosclerotic plaques present
10	1893	Brannan[11]	73	M	Sudden attack of hematemesis		A second attack 2 days later was fatal	Aneurysm above renal artery adherent to and perforating third part of duodenum. Aneurysm filled with thrombus. Marked arteriosclerosis present throughout
11	1895	Foá[12]	28	M	Three months before, penile ulcer. Inguinal abscess 2 weeks before admission. One week, lumbar pain	Epigastric mass felt	Sudden hematemesis day after admission and death in a few minutes	Perforation of aorta 2 cm. below renal arteries, leading into a false aneurysm which was adherent and had perforated into third part of duodenum. Streptococci were found in adventitia and surrounding tissues in region of perforation
12	1899	Boinet[13]	28	M	Abdominal and lumbar pain	Expansile epigastric mass	Few weeks after admission had hematemesis, and rapid death	Egg-sized aneurysm lying above the superior mesenteric, adherent and perforating third portion of duodenum
13	1905	Locke[14]	81	M	Severe lumbar pain, 3 months	Oval, pulsating epigastric mass	Sudden hematemesis, recurring 3 days later, and then death	Saccular aneurysm of abdominal aorta, partly filled with thrombus. It was adherent to, and had perforated, third portion of duodenum
14	1911	Celles and Jeanneney[15]	61	M	Sudden hematemesis	Strongly pulsating mass felt in epigastrium	Death in 2 days	Aneurysm just above bifurcation of aorta, adherent to, and perforating, the jejunum
15	1913	Zypkin[16]	45	M	Syphilis 12 years. Weakness, epigastric pain, melena	Tender, pulsating epigastric mass. Thrill felt. Murmur heard	Repeated, severe epigastric pain, tarry stools. Death in 8 days after admission	Walnut-sized aneurysm on anterior wall of aorta, adherent to, and perforating, stomach. Microscopic examination showed syphilitic mesaortitis

TABLE I—CONT'D

	DATE	AUTHOR	AGE	SEX	PERTINENT HISTORY LEADING TO ADMISSION	CLINICAL OBSERVATIONS	COURSE	PATHOLOGIC CHANGES
16	1914	Tozer[17]	32	M	Gradual onset of abdominal pain, getting progressively worse	Mass with expansile pulsation, seen and felt above and to left of umbilicus	One month after admission, hematemesis and rapid death	Saccular aneurysm arising below inferior mesenteric artery, perforating third portion of duodenum. Microscopic examination showed evidences of tuberculosis of aorta
17	1918	Marlow (Case 1) and Doubler[18]	39	M	Abdominal pain 6 months, weakness. Sudden onset of shock, hematemesis, and melena	Pulsating epigastric mass	A month later, second attack of hematemesis and death	Aneurysm, anterior wall of aorta, perforating into third portion of duodenum
18	1918	Marlow (Case 2) and Doubler[18]	81	M	Sharp pain in back	Pulsating abdominal mass	Sixteen days after admission had hematemesis and died	Aorta below renal arteries contained two aneurysms. One was adherent to, and perforated, third portion of duodenum
19	1921	Gerlach[19]	20	F	Sudden hematemesis and death		Died promptly after onset of hematemesis	Mycotic saccular aneurysm, arising below superior mesenteric artery, was adherent to, and perforating, third portion of duodenum
20	1926	Kern[20]	49	M	Acute otitis media 5 months before admission, healing in 2 months. Continuous fever, fatigue, and lumbar pain since		Low-grade fever, with rises to 104°. Three weeks after admission severe hematemesis and death in 2 hours	A saccular aneurysm was found below superior mesenteric artery. Its surface was partially covered with thrombus. It was adherent to, and had perforated, third portion of duodenum
21	1928	Messary and Flandrin[21]	53	M	Abdominal mass several months. Sudden hematemesis. History of syphilis and gumma of the testicle	Expansile, pulsating mass	Repeated hematemesis. Severe abdominal pain and death on seventh day	Aneurysmal dilatation adherent to, and perforating, third portion of duodenum
22	1928	Ahava[22]	56	M	Syphilis at 21. Pulsating mass and severe pain in left upper quadrant, 6 months	Tender, pulsating mass	Recurrent hematemesis and death in 6 weeks	Aneurysm of abdominal aorta perforating the duodenum

23	1930	Feller[24]	27	M	Periodic furunculosis, sore throat, vomiting, and melena		Repeated vomiting and melena; death in 9 days	Mycotic aneurysm at level of celiac axis adherent to, and perforating, the stomach
24	1931	Pescador and Villanueva[23]	32	F	Sudden hematemesis	Epigastric mass, murmur, and thrill. Serologic reaction positive	Repeated hematemesis; death on seventh day	Aneurysm of aorta adherent to cardia of stomach with perforation into it
25	1931	Riggs and Massey[25]	69	M	Weakness and backache 8 months. Sense of burning in epigastrium 2 months. Sudden melena	Epigastric mass. Serologic reaction negative	Day after melena went into shock and died	Saccular aneurysm 2 cm. above bifurcation, filled with thrombus, adherent to, and perforating, the duodenum
26	1936	Scully[26]	62	M	Entered hospital with malaria		Month after admission, abdominal mass developed, also severe abdominal pain, melena, shock, and death	Saccular aneurysm, adherent to duodenum. Perforation into third portion
27	1936	Kampmeier[27]			No data	No data	No data	Aneurysm of celiac axis rupturing into stomach
28	1937	Manson[28]	76	M	Found in shock	Pulsating mass in epigastrium	Death in 2 days	Saccular aneurysm of anterior wall, adherent to, and perforating, third portion of duodenum
29	1937	Neely (Case 3)[29]	59	M	Intermittent dysuria, frequency, nocturia	Pulsating mass in right flank	Sudden shock and hematemesis; death in 2 days	Aneurysm of lower abdominal aorta ruptured into retroperitoneum, producing a false aneurysm which in turn became adherent to, and perforated, third portion of duodenum
30	1939	Roach[30]	52	F	Long history of digestive trouble typical of peptic ulcer. More recently, severe epigastric pain and hematemesis		Repeated hematemesis and death	Abdominal aorta was markedly calcified. Aneurysm present, eroding third portion of duodenum
31	1941	Smith[31]	77	M	One week, indigestion and vomiting. Hematemesis day before admission	Pulsating mass to right of umbilicus	Two hours after admission, shock and death	Marked arteriosclerosis of aorta, with a saccular aneurysm, filled with thrombus, adherent to, and perforating, third portion of duodenum

dominal aneurysm, should be considered, although in this particular case very little atherosclerosis was found. There is a possibility, of course, that it might have been particularly severe at the site of aneurysm formation, and subsequently became obscured by ulceration and thrombus formation. This, however, would be most unusual, for it is the rule that atherosclerosis is present to a rather severe degree both in and beyond the aneurysm, and remains detectable despite thrombus formation. A final possibility is mycotic aneurysm. The presence of organisms in our case complicates rather than clarifies matters. Unfortunately, cultures were not made, so that one has only morphologic criteria for identification of the bacteria. They were large, Gram-positive bacilli, some of which contained spore-like vacuoles. The resemblance to *B. subtilis* was close. The problem is made more perplexing by the fact that the organisms were found in the wall of the aneurysm and on the surface of the thrombus which filled it, and in no other place in the body, thus eliminating the possibility of ante- or post-mortem bacteremia. A probable reason for the peculiar localization is that the organism reached the aneurysm via the duodenal perforation. More suggestive of a mycotic origin is the fact that there was an antecedent history of pneumonia, complicated by empyema, and later by destructive arthritis of the hip joint. It was during a three months' stay in bed for this condition that the aneurysm was discovered and subsequently seen to grow and finally to rupture. Unfortunately, we were not able to demonstrate cocci. Of the cases collected (Table I), in only four was the aneurysm reported as mycotic.[12, 19, 20, 24] The stories of these are as follows:

Case of Foá:[12] The patient was a 28-year-old man. A week before admission he had a right inguinal abscess, fever, and pain in the lumbosacral area. After incision and drainage the abscess healed, but the pain persisted. Physical examination disclosed a tender, protuberant abdomen. An orange-sized mass was felt in the epigastrium. After four days of diarrhea he vomited blood and died. Necropsy disclosed a false aneurysm which communicated with the aorta on the one hand, and the third portion of the duodenum on the other. Microscopic examination disclosed streptococci throughout the adventitia, in the periaortic tissue, in the walls of the aneurysm, and in the serosa of the duodenum. Small abscesses were also found in the adventitia of the aorta. The author concluded that, with the inguinal abscess as a focus, the infection spread to the prelumbar lymphatics, producing a periaortic cellulitis which, in turn, infected the wall of the aorta and led to aneurysm formation.

Case of Gerlach:[19] The report concerned a 20-year-old woman. She had abdominal pain and died of hematemesis. Autopsy revealed a saccular, false aneurysm between the superior and inferior mesenteric arteries; it was adherent to the duodenum and had ruptured into it. Because of a history of throat infection shortly before, the patient's youth, and the lack of other etiologic factors, it was concluded that the aneurysm was mycotic.

Case of Kern:[20] The patient was a 49-year-old man who developed acute otitis media with a high fever. The condition persisted for two months. After this he continued to be weak, had low-grade fever, and developed a burning pain in the lumbar region. Three weeks before admission he developed an intermittent fever which reached 104° F. Physical examination failed to disclose a focus of infection. After a febrile course of three weeks he began to vomit blood and died. At the

autopsy an abscess containing about two ounces of pus was found in the region of the bifurcation of the aorta. At this point the wall of the aorta tore easily. In addition, an opening, 2½ × 3½ cm., was found higher up in the aorta, and led into an aneurysm. The latter, in turn, was adherent to the third portion of the duodenum and communicated with its lumen. The author was not sure of the cause of the aneurysm in this case. He felt that it might be mycotic.

Case of Feller:[24] The patient was a 27-year-old man who was operated on for duodenal ulcer. He subsequently died. Autopsy disclosed an aneurysm above the celiac axis which was adherent to, and communicated with, the stomach. Microscopically, Gram-positive cocci, in chains, were discovered in the fibrin and polymorphonuclear leucocytes which covered the inner surface of the aneurysm. The author concluded that the aneurysm was mycotic in nature. Later, he obtained a history that the patient had had furunculosis one and one-half years before, and, a year later, tonsillitis. Five months after this he developed severe backache and fever.

Since only these four cases have been reported, it is apparent that rupture of a mycotic abdominal aneurysm into the gastrointestinal tract is rare. Careful scrutiny shows that in only two of the above cases was the diagnosis apparently proved; in the others it was doubtful. It is possible that our case falls in the doubtful group.

Regardless of cause, other features of the case are of interest. One of these is the fact that the usual site for rupture into the gastrointestinal tract is the third portion of the duodenum. The reason for the particular predilection for this part of the intestine lies in the fact that it is relatively fixed, so that it is not as easily displaced by a gradually enlarging tumor as are the stomach and small intestine. The pressure of the aneurysm produces irritation which leads to fibrous adhesions, and, eventually, to focal necrosis of the duodenum. Subsequently, digestive juices probably play a part in accelerating the perforation of the one organ into the other.

SUMMARY

1. Thirty-one cases of rupture of an abdominal aneurysm into the stomach and duodenum were collected from the literature.

2. The clinical and pathologic data on these cases are presented in table form.

3. Four cases of what was probably mycotic aneurysm were collected from the literature and are described.

4. Another case of aneurysm which may have been mycotic is reported; in this instance the aneurysm ruptured into the duodenum.

REFERENCES

1. Chamel and Dalmas: Dictionnaire de Medecine, Tome III, Paris, 1833.
2. Salmon: Anevrysme de l'aorte ventrale mort par rupture de la poche arterielle dans le duodenum, Bull. Soc. anat. de Par. **18**: 283, 1843.
3. Johnson, G.: Aneurism of the Abdominal Aorta, Fatal by Sudden Hemorrhage, Brit. M. J. 204, 1859.
4. Seligman, L.: Aneurysma der Brust- und Bauchaorta, Tuberculose der Lunge, Durchbruch der Aortenwand, Wien. med. Wchnschr. **12**: 15, 1862.
5. Stich, E.: Duodenal Geschwür mit Durchbruch in die Aorta Abdominalis, Deutsches Arch. f. klin. Med. **13**: 191, 1874.

6. Von Vehling, C.: Perforation der Aorta in den Digestions Tract, Inaug. Diss. der Universität Erlangen, 1878.
7. Coupland: Abdominal Aneurysm Rupture Into Duodenum, Med. Times & Hosp. Gaz. **2**: 65, 1883.
8. Dickenson, W. L.: Aneurysm of Abdominal Aorta Compressing Common Bile Duct and Rupturing Into Duodenum, Tr. Path. Soc. Lond. **42**: 76, 1891.
9. Bailey, T. R.: Notes on a Case of Aneurysm of the Abdominal Aorta, Lancet **2**: 12, 1891.
10. Bernacchi, L.: Sopra un caso di aneurisma dell' aorta abdominale perforatosi nel duodeno, Atti. d. Ass. med. lomb. 174, 1891-92.
11. Brannan, J. W.: Rupture of Aneurysm of Abdominal Aorta in Duodenum, Proc. N. York Path. Soc. **43**: 76, 1893.
12. Foá, P.: Aneurisma Spurio per peri aoritico D'origine infettiva, Gior. d. r. Accad. di med. di Torino **5**: 374, 1895.
13. Boinet: Anevrysmes d'l aorte, Arch. prov. de méd. 412, Case 12, 1899.
14. Locke: Four Unusual Cases of Aneurysms, Boston M. & S. J. **153**: 659, 1905.
15. Celles, and Jeanneney: Rupture d'un anevrysme de l'aorte abdominale dans le jejunum, J. de méd. de Bordeaux **14**: 315, 1911.
16. Zypkin, S. M.: Aneurysm of the Abdominal Aorta Opening Into the Stomach Through a Round Ulcer, Deutsche med. Wchnschr. Berlin **39**: 1145, 1913.
17. Tozer, E. A.: A Case of Tuberculous Aneurysm of the Abdominal Aorta With Rupture Into the Duodenum, Brit. M. J. **2**: 1022, 1914.
18. Marlow, S. B., and Doubler, F. H.: Aneurysm of the Abdominal Aorta With Rupture Into the Duodenum, Am. J. M. Sc. **155**: 540, 1918.
19. Gerlach: Wiederholte Perforation eines mykotischen Aneurysmas der Bauchaorta ins Duodenum, München. med. Wchnschr. **68**: 502, 1921.
20. Kern, J.: Ueber einem Fall von Durchbruch eines Aneurysmas der Bauchaorta ins Duodenum, In. Diss. Tubingen, 1926.
21. Messary, E., and Flandrin: Anevrisme de l'aorta abdominale fissure dans le duodenum, Soc. med. des hôp. de Par. **53**: 1205, 1928.
22. Ahava, V.: Ein das Duodenum perforierende Aneurysma abdominalis, Duodecim **44**: 486, 1928.
23. Pescador, L., and Villanueva, S.: Perforation of Abdominal Aneurysm of the Aorta Into Stomach, Arch. cardiol. y hemat. **12**: 247, 1931.
24. Feller, A.: Magenblutung aus ungewöhnlicher Ursache, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**: 671, 1930.
25. Riggs, T. F., and Massey, B. D.: Aneurysm of the Abdominal Aorta Which Terminated by Rupture Into the Duodenum, Journal-Lancet **51**: 413, 1931.
26. Scully, F. J.: Rupture or Aneurysm of Abdominal Aorta Into the Small Intestine, Tri-State M. J. **9**: 1743, 1936.
27. Kampmeier, R. H.: Aneurysm of the Abdominal Aorta, a Study of 73 Cases, Am. J. M. Sc. **192**: 97, 1936.
28. Manson, J. S.: Rupture of Aorta Into the Duodenum, Brit. M. J. **1**: 121, 1937.
29. Neely, J. M.: Ruptured Abdominal Aorta, Clinico Path. Study of 5 Cases, Nebraska M. J. **22**: 370, 1937.
30. Roach, R. D.: A Rare Cause of Fatal Hemorrhage, Canad. M. A. J. **41**: 173, 1939.
31. Smith, H. M.: Aneurysm of the Abdominal Aorta. Report of a Case, Rupture Into the Duodenum, Virginia M. Monthly **68**: 270, 1941.

CONGENITAL SUBAORTIC STENOSIS, WITH DEFORMITY OF THE AORTIC VALVE

Report of a Case With Complicating Subacute Bacterial Endocarditis and Mycotic Aneurysm Resulting in Rupture of the Aorta Into the Pericardium

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AMONG the rarer types of congenital heart disease is subaortic stenosis. Abbott[1] described twelve instances among one thousand cases of congenital heart disease. Wiglesworth[2] found only thirty-six in a review of the literature prior to 1937, to which he added one case. No instances of this congenital anomaly have been found in more than ten thousand autopsies at the Massachusetts General Hospital.[3] Because the reported cases of subaortic stenosis are so few, and because subaortic stenosis may be confused clinically with acquired aortic valve disease, chiefly rheumatic in type, as it was in this case, we are adding this report to the literature. Congenitally deformed aortic valves, per se, are occasionally seen at post-mortem examination, but we have found in the literature only one other case in which a congenitally deformed (bicuspid) aortic valve was associated with subaortic stenosis. In that case, reported by Thursfield and Scott,[4] there was probably, also, slight coarctation of the aorta. It is of further interest that the death of our patient was the result of cardiac tamponade from rupture of a mycotic aneurysm within the pericardial sac.

CASE REPORT

Mrs. C. was first seen by one of us (P. D. W.) in 1929, at the age of 17 years, when a diagnosis of rheumatic, or, possibly, congenital, heart disease, aortic stenosis, and slight aortic regurgitation was made. There was no clear-cut history of rheumatic fever. She was examined for the second time ten years later, during the early part of pregnancy. The heart was essentially the same as ten years before. Pregnancy was borne without difficulty, and she was in excellent health in April, 1939, after the forceps delivery of a healthy baby. She continued well, leading a moderately active life without discomfort, until April, 1940, when there appeared, two weeks after extraction of a tooth, unusual fatigue, chills and fever, and diarrhea. There developed considerable pain, tenderness, and swelling of several large joints. She was studied carefully in order to ascertain the nature of the infection, and a diagnosis of subacute bacterial endocarditis was made, with positive *Streptococcus viridans* blood cultures, some weeks thereafter. She was given sulfapyridine, but did not tolerate it well, and the drug was discontinued because of much nausea and vomiting and the development of moderately severe anemia. The course of the disease was a slowly progressive one. She showed increasing pallor, continuous fever, and severe asthenia.

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On Jan. 6, 1941, she was seen by one of us (B. J. W.) because of the sudden onset of severe pain beneath the upper part of the sternum and left clavicle. On examination she showed numerous petechiae, particularly over the soles of the feet and in the conjunctivae, marked pallor, and scattered pulmonary râles, particularly on the left side, behind the heart. There was moderate enlargement of the liver; this had not been present before. The spleen was readily palpable, as it had been since April, 1940. There was no edema or shortness of breath. She was able to lie flat without distress. On examination of the heart there was heard a loud, rough systolic murmur, maximal in the aortic area to the right of the sternum, but well heard over the entire chest, and accompanied by a thrill. There was a slight blowing diastolic murmur along the left sternal border. The heart was much enlarged; the apex impulse was visible 11 cm. to the left of the midsternal line in the fifth intercostal space. The aortic second sound was present, but greatly diminished. The blood pressure measured 100/70.

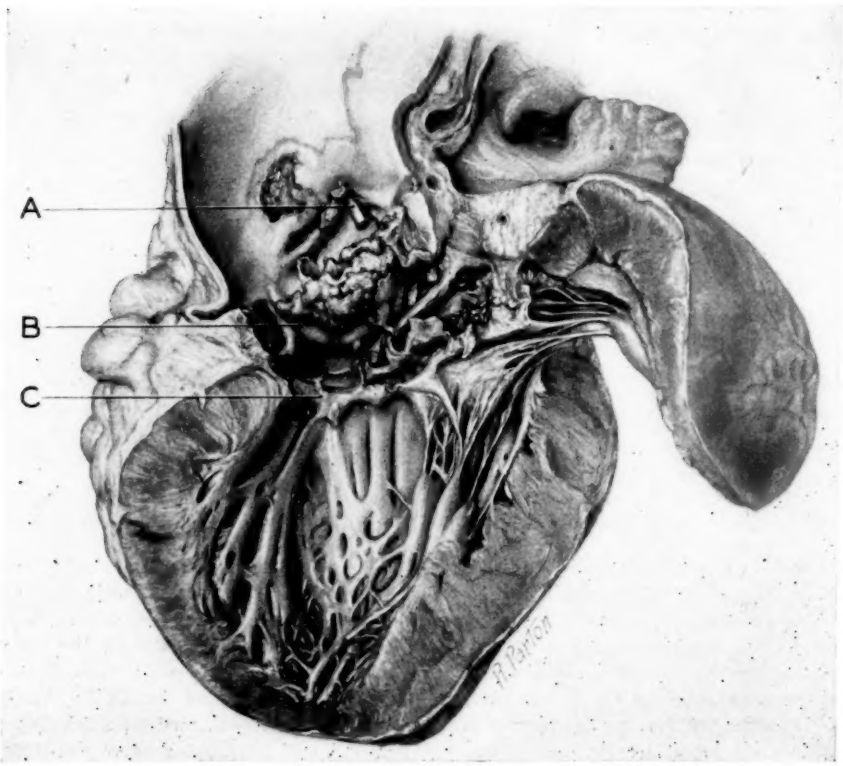

Fig. 1.—Drawing of opened left ventricle and first part of aorta. *A*, Internal opening of mycotic aneurysm, with probe inserted. *B*, Aortic valve, with vegetations. The arrow points to the large posterior cusp, on each side of which there are small anterior cusps separated by an elongated raphe which is hidden at the left-hand side of the drawing; about half of each anterior cusp is visible in the drawing, flanking the large posterior cusp. *C*, Subaortic shelf.

Death occurred suddenly twenty-four hours later, apparently not preceded by pain or other unusual circumstance.

Autopsy was performed five and one-half hours after death. When the thoracic plate was removed, there was evident a bluish color of the pericardium. The pericardium was opened, and 500 c.c. of blood were found therein, mostly in a large clot.

The heart and lungs were removed, and, after careful search, there was found, about 2.5 cm. above the aortic ring, a small aneurysmal dilatation of the aorta 2.5 cm. in length, at one end of which was a point of rupture from which blood could be expressed. The rupture was about the size of the end of a probe. Freed of the blood in the pericardium, the heart weight was approximately 425 grams.

The heart was opened, first into the left auricle, which seemed slightly dilated. Just above the mitral valve there was a small group of firm vegetations about the size of a pea. The valve leaflets and the remainder of the valve were entirely normal. There were no evidences of auriculitis. When the left ventricle was opened a considerable degree of infundibular stenosis was found 1.5 cm. below the insertion of the aortic valve; this was accentuated still further by a firm, raised fibrous ridge, 4 mm. wide and 4 mm. high, encircling the vestibule of the aorta and resulting in the formation of a small chamber between the aortic cusps and the subaortic shelf. There was a considerable mass of friable, irregular vegetations attached to the aortic valve cusps, and small clumps of the same type were found on the subaortic shelf. The probe was pushed gently through the external orifice of the aortic rupture, and protruded into the lumen of the aorta through the interior opening of a mycotic aneurysm which had developed beneath a plaque of vegetations about 2 cm. above the posterior cusp of the aortic valve. The left ventricle was considerably thickened; its wall measured about 15 mm. in section. The aortic valve was congenitally deformed; there were one very large posterior cusp, about 3 cm. in width, and two small anterior cusps of about equal size (1½ cm. each), which were equal to, or a little smaller than, the one large cusp. The coronary mouths were normally placed, one behind each of the anterior cusps. The valve, where it was free of vegetations, appeared normal, without evidence of rheumatic infection, past or present. The valvular endocarditis was preponderantly situated on the large posterior cusp.

The lungs were dry and entirely normal, except for a small area of atelectasis in the left lower lobe. There was no evidence of pericarditis or pleuritis. There were 500 c.c. of clear yellow fluid in the right pleural cavity.

The liver was considerably enlarged (estimated weight, 2,500 grams), and purplish-red; section showed that it contained an increased amount of blood. Otherwise the appearance was normal.

The spleen was much enlarged (estimated weight, 600 grams). There was a large, pyramid-shaped, healed infaret on the diaphragmatic surface of the spleen.

The kidneys did not appear remarkable except for two or three old infarcts. The bowel was removed and opened; it revealed nothing unusual.

Microscopic examination showed numerous collections of inflammatory cells in the myocardium. In some areas these were so numerous as to constitute abscesses. No definite Aschoff bodies were seen. There were the usual microscopic changes associated with areas of infarction in the spleen and kidney. There was marked chronic passive congestion of the liver. No histologic studies were made of the subaortic shelf or of the aortic valve. Nothing else of importance was found.

DISCUSSION

There has been some controversy concerning the nature and origin of the firm, raised ring of tissue beneath the aortic valve which gives rise to the anomaly known as subaortic stenosis. The most reasonable explanation seems to be that presented by Sir Arthur Keith,[5] in whose opinion this firm, raised band is of congenital origin and represents a remnant of the bulbus cordis. Histologic evidence in the case described by Wiglesworth is in keeping with this point of view.

Subaortic stenosis may be suspected in patients under 20 years of age when there is no clear-cut history of rheumatic fever and the patient presents the auscultatory signs of well-developed aortic stenosis and a normal or nearly normal aortic second sound, for acquired stenosis of the aortic valve seldom occurs in patients under the age of 20 years. In the presence of these signs, the younger the patient, the more likely is the diagnosis of congenital subaortic stenosis to be correct.

The slight diastolic murmur along the left sternal border in our case probably resulted from the deformity of the aortic valve, for slight aortic regurgitation may have been present, although, as a rule, a bicuspid aortic valve does not produce a murmur. This was apparently true in the case described by Thursfield and Scott,[4] for, in their report of a case of bicuspid aortic valve and subaortic stenosis, no diastolic murmur was mentioned.

SUMMARY

A case of congenital subaortic stenosis, with a congenitally deformed aortic valve, is described; the patient was a woman who died, at the age of 29 years, of subacute bacterial endocarditis, with a ruptured mycotic aneurysm of the aorta and cardiac tamponade. We believe that a correct diagnosis of congenital subaortic stenosis is possible in patients under the age of 20 years who show clinical evidence of aortic stenosis, with a normal or nearly normal aortic second sound.

We are indebted to Dr. Eugenia E. Murphy, of Arlington, Va., for her cooperation concerning this case.

REFERENCES

1. Abbott, Maude E.: Atlas of Congenital Cardiac Disease, published by the American Heart Association, 1936.
2. Wiglesworth, F. W.: A Case of Sub-Aortic Stenosis With Acute Aortic Endocarditis, J. Tech. Methods **17**: 102, 1937.
3. Mallory, Tracy, and Castleman, Benjamin. Personal Communication, July, 1941.
4. Thursfield, H., and Scott, H. W.: Sub-Aortic Stenosis, Brit. J. Child. Dis. **10**: 104, 1913.
5. Keith, Sir Arthur: Schorstein Lecture on the Fate of the Bulbus Cordis in the Human Heart, Lancet **2**: 1267, 1924.

Abstracts and Reviews

Selected Abstracts

Eggleton, M. G., Richardson, K. C., Schild, H. O., and Winton, F. R.: Renal Impairment Due to Crushing Limbs in Anaesthetized Dogs. Brit. M. J. 2: 392, 1942.

So far as available evidence goes, the injury to the kidneys in this series of dogs appears to be of the same kind as that in man after comparable prolonged crush injury to the limbs. The essential nature of the renal damage has not yet been determined, but the evidence suggests that the main factor may be concerned with increase in permeability of the renal tubules due to a toxic agent released from the damaged limbs, while there may be an additional factor involving reduction in the rate of glomerular filtration probably due to lowering of glomerular capillary pressure.

AUTHORS.

Davies, F.: The Conducting System of the Vertebrate Heart. Brit. Heart J. 4: 66, 1942.

The specialized muscle fibers comprising the conducting system of the hearts of mammals and birds include S-A node, A-V node, A-V bundle and its two limbs, and terminal ventricular subendocardial and penetrating Purkinje fibers. Added to these in the bird's heart are the atrial subendocardial and penetrating Purkinje fibers, the right A-V ring, and the special branch of the right limb of the A-V bundle to the muscular A-V valve.

While the main topography of this system is similar in mammals and birds, differences are correlated with functional requirements.

The specialized cardiac conducting system of these homoiothermal vertebrates is not a remnant of more extensive tissues of similar structure in lower vertebrate hearts. It is a neomorphic development, associated with the more rapid rate of the heart (more rapid, in proportion to its size). Ontogenetic development of these structures in the mammal (calf) supports this view.

In a lowly generalized vertebrate heart (salamander) no specialized tissue is present. The sequences of the cardiac cycle are similar to those of the higher vertebrates. Each chamber has its own intrinsic rhythmic rate, the reason for which is not clearly established. The glycogen content of the musculature of the heart of the frog, which is also devoid of specialized tissue, is inversely proportional to the intrinsic rhythmic rates of the several chambers. In mammals and birds, parallel evolution of the specialized conducting system has taken place; small differences in the topography of the specialized conducting fibers in closely allied species, or in different animals of the same species, may be attributed to variation.

AUTHOR.

Sharpey-Schafer, E. P., and Wallace, J.: Circulatory Overloading After Rapid Intravenous Injections. Brit. M. J. 2: 304, 1942.

Up to 2,000 c.c. of saline, serum, and blood was injected into subjects without cardiovascular disease at rates of from 54 to 168 c.c. a minute. The venous pressure was raised up to 11 cm. H_2O when there was considerable retention of injected fluid in the circulation, as indicated by the fall in hemoglobin. Radiographs showed an increase in the diastolic size of the heart, enlargement of the pulmonary arteries, and prominence of the vascular markings in the lung fields. Vital capacity was diminished, but there was no evidence of pulmonary edema. In spite of the rise of venous pressure many subjects had no increase in heart rate. Of twelve subjects four showed electrocardiographic changes indicating slight right heart stress. Symptoms were absent or unimportant. There was a rapid fall of venous pressure to normal on ceasing injection, except in one subject given blood. There is evidence that the peripheral and pulmonary capillaries and veins dilate to accommodate the increased blood volume.

When the blood volume was first reduced by a large venesection, saline or serum injected in similar amounts and at similar rates caused little or no rise of venous pressure.

AUTHORS.

Hass, G. M.: Elastic Tissue. II. A Study of the Elasticity and Tensile Strength of Elastic Tissue Isolated From the Human Aorta. Arch. Path. 34: 971, 1942.

In a series of twenty-one human aortas, aged 10 days to 77 years, the amounts of elastic tissue which were recovered varied from 28.9 to 42.2 per cent, with an average of 37.9 per cent.

The quantity of elastic tissue in each unit volume of the average aortic wall remains nearly constant throughout life. Individual variations are included in the range 28.9 to 42.2 per cent.

The purified elastic systems possess an average of 32 per cent greater extensibility and 170 per cent greater retractility than the intact aortic walls from which they are isolated.

The average maximum extensibility of isolated elastic tissue decreases with increasing age in a manner which cannot be predicted by a study of the intact aorta.

The retraction of isolated elastic tissue after extension is always more complete than that of the intact vessel. The magnitude of retraction is the same for all isolated networks and is independent of their age.

The tensile strength of isolated tissue varies from 1,490 to 6,750 Gm. per square centimeter of dry cross-sectional area at maximum extension. In general, tensile strength decreases with increasing age. There are several unexplained exceptions to this average rule.

AUTHOR.

Henry, F.: Cardiovascular Effects of Experimental Insomnia. Am. J. Physiol. 138: 65, 1942.

The mean heart rate of eight male human subjects was lowered at rest in the reclining posture but not while standing, as the result of twenty-four hours of sleep deprivation. It was also lowered during exercise and recovery. An increased negative phase was observed, and there was also a reduction in the amount of relative bradycardia produced by a modified Valsalva experiment performed during early recovery from exercise. A reduced irritability of some part of the mechanisms responsible for rate control during late exercise and recovery is postulated in explanation.

Scores on the Foster, pulse-ratio, and McCurdy-Larson cardiovascular tests were markedly improved as a result of the insomnia. The Schneider index was also raised, but the increase was not statistically significant.

Kisch, B., Goldbloom, A. A., and Zucker, G.: Electrocardiographic Changes After Occlusion of the Pulmonary Artery or Aorta. Cardiologia 6: 83, 1942.

Experiments are presented in which an acute increase in pressure in one ventricle was produced by clamping the pulmonary artery or aorta. Typical electrocardiographic changes were observed.

These electrocardiographic changes are similar to those recently described after a potassium chloride blotting paper was placed on an isolated area of the right or left side of the heart respectively. These findings seem to indicate that in these experiments a damage of predominantly one side of the heart is present.

No electrocardiographic changes were obtained in the authors' experiments when one hilus or when less than two-thirds of the pulmonary artery was clamped.

AUTHORS.

Kisch, B.: A Contribution to the Problem of the Electrical Alternation of the Heart. Cardiologia 6: 95, 1942.

It is shown that the presence of alternation in the electrocardiogram depends in the same way on exactly the same factors as the mechanical alternation of the heart manifest in the tracings of heart beat and pulse wave.

These important factors are the bioenergetic condition of the heart (disposing factor), the heart rate, the blood pressure and the extracardiac nerves of the heart.

There is no reason to look at the electric alternans as a separate phenomenon of the heart pathology as was repeatedly done in the literature of the last years.

A satisfactory explanation of the isolated electric alternans is given by recent findings that only or predominantly the surface layer of the heart muscle is shaping the ecg. from the peak of R up to the end of T.

A tracing is presented which shows an alternating A-V conducting time in a cat's heart.

AUTHOR.

Nylin, G., and Crafoord, C.: Simultaneous Electrograms From Left and Right Ventricles of the Human Heart. Cardiologia 6: 136, 1942.

Simultaneous, selective (unipolar) electrograms of the right and left ventricles of the freed human heart with intact pericardium give potential and typical dextro- respectively sinistrograms opposed to each other.

AUTHORS.

Dagnini, G.: Gallop Rhythm and Atrioventricular Dissociation. Cardiologia 6: 146, 1942.

Description of three unusual forms of gallop rhythm caused by atrioventricular dissociation. The author suggests the first form be termed retarded proto-diastolic gallop, the second variable proto-meso-tele-diastolic gallop and the third variable pre-diastolic-meso-proto-diastolic gallop. Each term gives the characteristic beat in the acoustic sense, as also the special aspect expressed in the tonogram. The first type is observed with partial A-V block of the type 2:1, the second with complete A-V dissociation, the third with partial block with Wenckebach-Luciani's periods.

The conditions under which each form arises are enumerated and individual points, which partly explain the genesis of the tones connected with the disturbances mentioned, are emphasized.

AUTHOR.

Edeiken, J.: Extreme Tachycardia: With Report of Non-Fatal Paroxysms Following Myocardial Infarction. Am. J. M. Sc. **205**: 52, 1943.

Two cases of extreme tachycardia are added to the fifteen cases previously reported with a recorded ventricular rate of 300 or more per minute; in one instance the tachycardia occurred during the acute stage of myocardial infarction.

So far as can be determined, Case 1 is the only case in which such extreme tachycardia was recorded in the presence of acute myocardial infarction; in the other cases of extreme tachycardia the myocardium was regarded as sound.

Two paroxysms of extreme tachycardia occurred in the patient suffering from myocardial infarction—one lasting twelve hours with a ventricular rate of 310 per minute, and another lasting thirty-four and one-half hours with a ventricular rate of 303 per minute. The onset and offset in both attacks were sudden.

The ventricular rate of 310 per minute is the fastest sustained tachycardia recorded in the adult human heart; more rapid rates have been recorded in infants.

In nine of the fifteen previously reported cases, treatment did not appear to influence the paroxysms or prevent their recurrence. It is questionable whether treatment (quinidine and digitalis) exerted any beneficial effect in stopping paroxysms complicating acute myocardial infarction.

AUTHOR.

Toledo, P. de A.: Sinoauricular Block. Rev. argent. de cardiol. **9**: 111, 1942.

Numerous arguments, clinical, physiopathologic and experimental, are in favor of the existence of sinoauricular block. Following Spuehler, many electrocardiographic records of difficult interpretation may be considered as an example of this type of block.

Sinoauricular blocks may be classified in the same way as auriculoventricular blocks. They are generally reversible, of vagal or toxic cause or combination of both, and their differential diagnosis is facilitated by the exercise and atropine tests. Sometimes they coexist with other conduction disturbances in which case severe and diffuse myocardial lesions are probably present.

AUTHOR.

Vedoya, R., Videla, J. G., and Albanese, A. R.: Persistence of the Ductus Arteriosus. Surgical Intervention in Four Cases. Rev. argent. de cardiol. **9**: 94, 1942.

The results obtained by ligation of the ductus in four cases of patent ductus arteriosus are reported. Two of them were in bad condition when operated upon. The results were excellent in the three cases in which no other malformation was present. Marked reduction of the heart size a few days after operation, great improvement of functional capacity of the heart and beneficial effects on somatic and intellectual development were the salient features.

One case, in which a pulmonary stenosis was diagnosed during operation, died a few hours after of pulmonary embolism.

On discussing its indication, the conclusion is reached that operation should be tried in every case, and as early as possible.

AUTHORS.

Corner, B., and Perry, B.: Hemiplegia in Cyanotic Congenital Heart Disease. Brit. Heart J. 4: 121, 1942.

Three cases of cyanotic congenital heart disease developing sudden hemiplegia in infancy have been described. The possible mechanism of this has been discussed.

AUTHORS.

Cossio, P., Dambrosi, R. G., and Lezica, A. P.: Cardiac Aneurysm and Isolated Myocarditis. Rev. argent. de cardiol. 9: 182, 1942.

In a case of isolated myocarditis necropsy revealed the presence of a parietal aneurysm next to the apex of the heart. In the absence of other etiologic evidences, especially of coronary lesions, and considering the predominance of infiltrates at the level of the aneurysm, a relation of cause and effect between isolated myocarditis and aneurysm is established.

AUTHORS.

Cookson, H.: Fainting and Fits in Cardiac Infarction. Brit. Heart J. 4: 163, 1942.

Among two hundred patients with acute cardiac infarction, a syncopal or epileptiform attack was observed in fifteen. At the onset syncope occurred in ten, of whom five were aged 70 years or more. They presented the appearance of severe peripheral circulatory failure, often combined with a slow heart rate, but in one there was ventricular tachycardia. Pain might be absent or slight. In five, the cardiogram showed abnormal rhythms of supraventricular origin. Posterior infarction was commoner than anterior. Six of the patients had died by the fourth month. Possible causes of the syncope are briefly discussed.

Syncope and fits in the course of cardiac infarction are reported in five patients, whose average age was 69 years. Two had suffered previously from anginal pain. Two had syncope and three had Stokes-Adams attacks. All five died within twenty-nine days of onset. Abnormal rhythms were recorded in four. Cardiograms during the actual attack showed complete heart block in one, and nodal rhythm with a change in the ventricular complex immediately after a short convulsion in another. Indirect evidence as to the mechanism underlying the attacks in the remaining cases is given.

AUTHOR.

Rascoff, H.: Beriberi Heart in a 4-Month-Old Infant (With Four-Year Follow-Up). J. A. M. A. **120**: 1292, 1942.

In a case of beriberi heart in a 4-month-old infant the diagnosis was made clinically, and therapeutic response was noted with thiamine hydrochloride.

The daily diet of the average young infant is deficient in thiamine hydrochloride and should be supplemented with vitamin B_1. In cases of gastrointestinal disturbances the vitamin B_1 intake is to be increased.

Some cases at present diagnosed as idiopathic cardiac hypertrophy, or deaths attributed to status thymicolymphaticus, may be caused by infantile beriberi.

AUTHOR.

Kuttner, A. G., and Reyersbach, G.: The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide. J. Clin. Investigation **22**: 77, 1943.

Streptococcal upper respiratory infections and rheumatic relapses in rheumatic children were prevented by the prophylactic administration of sulfanilamide.

Toxic manifestations of sufficient severity to necessitate the withdrawal of the drug occurred in 15 per cent of the patients.

Children, who did not develop toxic reactions, tolerated the drug well.

The effectiveness of sulfanilamide in preventing rheumatic recurrences indicates that infection with Group A hemolytic streptococci is an important factor in the etiology of rheumatic fever.

AUTHORS.

Guion, C. M., and Adams, E. C.: Six Autopsied Cases of Disseminated Lupus Erythematosus. Am. J. M. Sc. **205**: 33, 1943.

The clinical, laboratory, and autopsy findings in six cases of disseminated lupus erythematosus observed at the New York Hospital between 1936 and 1940 are reported.

No common etiologic basis was observed in these six young women. Study of the diseased tissues cast no light on the pathogenesis.

While vascular lesions were observed, none of the cases resembled periarteritis nodosa. Noteworthy was the frequent association with acute and chronic arthritis and with pericarditis.

AUTHORS.

Christian, H. A.: Nonspecificity of Glomerular Lesions of the Kidney. Am. J. M. Sc. **204**: 781, 1942.

This paper has emphasized the nonspecificity of lesions observed in the glomerulus of the kidney and offers this nonspecificity as an explanation of many similarities in the signs and symptoms of renal diseases.

AUTHOR.

Howell, T. H.: Blood Pressure and Old Age. Brit. Heart J. **4**: 143, 1942.

A rise of systolic blood pressure is common after the age of 60 years.

In the present series of 120 Chelsea pensioners, 42 per cent had systolic figures regularly over 160 mm.

Cancer, cardiac failure, and infections often cause a fall in blood pressure.

Marked arteriosclerosis, in the absence of raised blood pressure, is usually associated with poor physical condition.

It is suggested that the raised blood pressure of old age is a form of compensation tending to prevent ischemia of vital structures.

AUTHOR.

Redish, J., and Chasis, H.: Function of the Separate Kidneys in Hypertensive Subjects. Arch. Int. Med. **70**: 738, 1942.

The impairment of renal parenchyma in hypertensive subjects proceeds in a parallel manner in both kidneys, the pace varying in different persons. The decrease in renal blood flow is shared equally by the two kidneys. In twenty-one subjects with essential hypertension selected at random unilateral renal ischemia was not found to be present in a single instance.

Absolute reduction in blood flow to one or both kidneys, as measured by diodrast clearance, does not necessarily demonstrate that renal ischemia is present. This conclusion can be drawn only if the tubular excretory mass is measured, so that the blood flow per unit of tubular excretory tissue can be evaluated.

Many common variations in ureteropyelograms are believed to be without significance. Pyelographic abnormalities are not necessarily associated with functional disparity, and conversely, marked functional disparity may not be associated with pyelographic abnormalities.

The rate of reabsorption of water by the tubules and hence the rate of urine flow may vary markedly in two kidneys of equal functional capacity. Excretory tests comparing the function of the two kidneys should therefore be evaluated with caution, for inequality in urine flow of itself can account for variations in specific gravity of the urine, in appearance time and relative concentration of dyes and in the roentgen shadows in excretory pyelography.

In three hypertensive subjects who had undergone surgical procedures for renal conditions significant disparities in the blood flow to the two kidneys were observed. In one subject who had undergone bilateral splanchnicectomy the blood flow was less than normal in both kidneys and markedly so in one. In two subjects who had had unilateral operations (omentopexy and nephropexy) the blood flow to the treated kidney was less than that to the untreated kidney. In none of the three subjects did the elevated arterial tension fall after surgical therapy.

AUTHORS.

Feldt, R. H., and Wenstrand, D. E. W.: The Family History in Arterial Hypertension: A Study of 4,376 Insurance Examinations. Am. J. M. Sc. **205**: 61, 1943.

A brief review of the literature and analysis of family histories taken from life insurance examinations are reported. In this series of 4,376 applicants, the incidence of familial cardiovascular disease was only slightly greater among hypertensive persons than it was among persons with normal blood pressure. There was no significant difference in the familial incidence of diabetes. It appears unlikely that heredity is of primary importance in the etiology of hypertension.

AUTHORS.

Lewis, T., and Stokes, J.: A Curious Syndrome With Signs Suggesting Cervical Arteriovenous Fistula, and the Pulses of Neck and Arms Lost. Brit. Heart J. **4**: 57, 1942.

A patient is described in whom the pulses of the neck and arms had been lost, and who presented signs suggesting an arteriovenous fistula at the root of the neck. The defective blood supply to the upper parts of the body was responsible directly or indirectly for a gross defect of vision, for frequent fainting attacks and headaches, and for pain in the right arm during work. The blood pressure in the patient's legs was raised.

Another case of a very similar kind is described, and a third recorded by Giffin is compared with them.

The three cases show so much in common as to suggest a pathological entity hitherto unrecognized and still awaiting dissection before its precise form can be understood.

AUTHORS.

Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa. Bull. Johns Hopkins Hosp. **71**: 123, 1942.

Vascular lesions characteristic of periarteritis nodosa have been found (1) in the viscera of five patients who, shortly before death, had had hypersensitive reactions following therapeutic injections of foreign serum. Four of these patients had received sulfonamides, but in at least two of those cases the evidence indicates that

the hypersensitive reaction was serum sickness and not drug sensitivity. The fifth patient had serum sickness in the absence of sulfonamide therapy; (2) in a biopsy of muscle from a patient who had a hypersensitive reaction following foreign serum and sulfonamide therapy; (3) in the viscera of a patient who had received prophylactic sulfonamide therapy against aspiration pneumonia.

None of these patients had had any symptoms suggestive of periarteritis nodosa prior to their terminal acute illness for which the serum or sulfonamide was administered, and the vascular lesions were fresh.

These cases, together with other pertinent evidence discussed in the body of this paper, indicate that vascular lesions of this type can be a manifestation of the anaphylactic type of hypersensitivity, and suggest the importance of a search for the inciting antigen in cases of periarteritis nodosa that come under clinical observation.

AUTHOR.

Master, A. M., Dack, S., and Jaffe, H. L.: Cardiac Efficiency and Prognosis Following Recovery From Acute Coronary Occlusion: The Results of Various Functional Tests. J. A. M. A. 120: 1271, 1942.

Cardiac efficiency was studied by various function tests performed serially on two hundred and two patients, who were observed for two to eight years following recovery from acute coronary occlusion. The results were evaluated from a prognostic point of view.

Recovery from acute coronary occlusion was found to be good or complete in over one-third of the patients; i.e., they had no symptoms of diminished cardiac reserve or routine activity. One-half were able to return to work, usually full time, and cardiac reserve, as measured by function tests, was normal or only slightly abnormal.

A persistent reduction in vital capacity was rare in the good recovery group, but common in those whose recovery was poor. However, the vital capacity not infrequently was normal in the presence of severe angina pectoris. A reduction below 2,000 c.c. was generally found only among patients who were in congestive heart failure.

The two-step exercise tolerance test, a simple nonstrenuous test of cardiac function, became normal in 18 per cent and remained distinctly abnormal in two-thirds of the patients. Return to normal usually occurred one or two years after the attacks, and was associated with a good clinical recovery and decreased incidence of subsequent attacks.

The teleoroentgenogram revealed definite cardiac enlargement in half of the patients, and the majority of these were hypertensive. As a general rule, chronic coronary sclerosis or coronary occlusion did not produce cardiac enlargement unless hypertension or heart failure was present. Although a severe degree of coronary disease may exist without cardiac enlargement, clinical recovery was more complete and subsequent attacks were less common when the heart size was normal, emphasizing the relation between heart size and cardiac function. Cardiac enlargement was always permanent.

A systolic expansion of the left ventricle, pathognomonic of previous infarction, was observed fluoroscopically or roentgenkymographically in nearly three-fifths of the patients, and localized absence or diminution of pulsation in 25 per cent. With few exceptions these abnormalities were permanent. Although an abnormal ventricular pulsation did not preclude a good recovery from the attack, it was almost universal in those whose recovery was poor. Not infrequently it was the only remaining sign of previous infarction, being observed in the majority of patients whose

electrocardiogram returned to normal. The patients with normal pulsations usually recovered completely, and rarely sustained another attack.

The electrocardiogram returned to normal or almost normal in 21 per cent of the patients, usually within one year after the attack. The great majority of these made a good recovery, as well as those whose T waves became normal although the Q waves persisted. However, the persistence of the findings characteristic of previous infarction, which was observed in almost two-thirds of the patients, was not necessarily a bad prognostic sign. The location of the infarct, i.e., whether anterior or posterior, did not affect the clinical course. However, when infarction of both surfaces had occurred, the prognosis was worse.

The electrocardiogram after the standard two-step exercise revealed signs of coronary insufficiency (depression of RS-T or inversion of T wave) in five of eighteen patients whose control record was normal, and in twenty-four of thirty-nine patients with abnormal electrocardiograms. A negative test was associated with a good recovery and good cardiac function.

The presence of a normal two-step exercise tolerance test, normal ventricular pulsation, or a normal electrocardiogram following coronary occlusion was usually accompanied by complete clinical recovery. Not only were significant angina pectoris and dyspnea uncommon when the foregoing tests became normal but a subsequent attack of either coronary occlusion or heart failure was rare. In those whose recovery was poor there was nearly always objective evidence of disability.

AUTHORS.

Perera, G. A., and Berliner, R. W.: The Relation of Postural Hemodilution to Paroxysmal Dyspnea. J. Clin. Investigation **22**: 25, 1943.

It has been confirmed that serum protein concentrations are considerably altered in health and disease by changes in position and by muscular activity.

This decrease in serum protein concentration appears to be the result of hemodilution, due to an increase in plasma volume.

The close correlation between nocturnal hemodilution and attacks of paroxysmal dyspnea suggests that an increase in plasma volume is an important factor in the production of acute left-sided failure in individuals with organic heart disease.

Clinical interpretations of protein values must be made with caution since an average fall of 0.8 Gm. per 100 c.c. is encountered after rest in the horizontal position.

AUTHORS.

Yeomans, A., Porter, R. R., and Swank, R. L.: Observations on Certain Manifestations of Circulatory Congestion Produced in Dogs by Rapid Infusion. J. Clin. Investigation **22**: 33, 1943.

Rapid infusion in dogs produced congestion in the peripheral, pulmonary and portal venous systems, evidenced by rises in their venous pressures; swelling of the abdomen, liver, and spleen, and in some cases, pulmonary edema; an increase in plasma volume and a dilution of the serum proteins; an increase in the heart rate, heart size, and cardiac output; gallop rhythm and systolic murmur; and an increase in oxygen consumption.

These phenomena and their relationship to congestive failure in humans are discussed. An explanation is offered for the stabilization of the peripheral venous pressure, which takes place during infusion.

AUTHORS.

Warren, S.: Effects of Radiation on Normal Tissues. VI. Effects of Radiation on the Cardiovascular System. Arch. Path. **34**: 1070, 1942.

An extensive review of the literature on the effects of roentgen radiation. This is a section of a more general review on other parts of the body. Includes as well the effect of radium and other active agents.

McCULLOCH.

Sigler, L. H.: Trauma of the Heart Due to Nonpenetrating Chest Injuries. J. A. M. A. **119**: 855, 1942.

Trauma of the heart and the adjoining structures caused by blows to the chest or to distant parts of the body occurs much more often than the literature would indicate. This paper describes briefly the results of the available experimental work on the subject, the types of force that may produce cardiac injury in man and the resulting form of injury. The symptom complex and electrocardiographic manifestations of cardiac injury are briefly described. Emphasis is placed on the importance of bearing in mind the possibility that trauma of the heart may occur in any bodily injury, and of subjecting such patients to frequent cardiac examinations, including repeated electrocardiographic studies.

AUTHOR.

Wakerlin, G. E., Johnson, C. A., Smith, E. L., Moss, W. G., and Weir, J. R.: Prophylactic Treatment of Experimental Renal Hypertension With Renin. Am. J. Physiol. **137**: 515, 1942.

Studies were made of the prophylactic effects of partially purified hog renin, inactivated hog renin, dog renin, rabbit renin, inactive human renin, and liver extract prepared like renin, in experimental renal hypertension in the dog.

Hog renin completely protected two dogs, partially protected one, and did not protect a fourth animal against the development of experimental renal hypertension following constriction of the renal arteries by the Goldblatt technique.

Inactivated hog renin protected one dog but did not protect three other animals.

Dog renin completely protected one dog, partially protected one, and did not protect two dogs.

Rabbit renin completely protected one dog against experimental renal hypertension.

Inactive human renin offered no protection to two dogs and liver extract was likewise ineffective in three dogs.

Sixteen untreated control animals all developed experimental renal hypertension following constriction of the renal arteries.

The mechanism of these prophylactic effects is not apparent at present. They may be due to renin or to some other substance in the partially purified renal extracts. Antirenin is almost certainly not involved. Further studies which may clarify the mechanism are now under way.

AUTHORS.

Burlingame, P., Long, J. A., and Ogden, E.: The Blood Pressure of the Fetal Rat and Its Response to Renin and Angiotonin. Am. J. Physiol. **137**: 473, 1942.

Injection of an effective dose of renin into the blood stream of rats in late pregnancy does not affect the fetal blood pressure. Injection of even larger doses of renin, angiotonin and adrenalin into the maternal blood stream cause a profound fall in fetal blood pressure. Recovery is slow and incomplete.

Injections of renin, angiotonin and adrenalin into the fetal blood stream cause a pronounced rise in fetal blood pressure.

With renin, tachyphylaxis was demonstrated in both mother and fetus independently but was not transferred from one to the other.

Injections of renin and angiotonin large enough to raise the maternal blood pressure when injected directly into the maternal circulation, fail to do so if injected into the fetal circulation.

The fetus is very much less responsive to renin, angiotonin and epinephrine than the mother.

AUTHORS.

Davidson, C. S., and MacDonald, H.: A Critical Study of the Action of 3-3′-Methlylenebis (4-Hydroxycoumarin) (Dicoumarin). Am. J. M. Sc. **205**: 24, 1943.

The effect of the synthetic compound 3-3′-methylenebis (4-hydroxycoumarin) —dicoumarin—upon the coagulation of blood and upon certain blood constituents was studied in detail in a small group of patients.

The drug was found to act by diminishing the effective prothrombin concentration in the blood, sometimes to very small amounts.

The prolonged blood coagulation time observed is apparently secondary to the low prothrombin concentration, but was not constant nor was it of marked degree unless large doses of the drug are administered.

The coagulation time measured in "Lusteroid," although more variable than in glass, showed much greater delay in clotting than in glass after the administration of the drug. The suggestion was made that the coagulation time in "Lusteroid" indicates the true coagulation defect more closely than does glass.

The occurrence of prothrombin clotting times longer than recalcified plasma clotting time was observed and the possible significance of the finding discussed.

The relation of the abnormal clotting mechanism to other coagulation factors: foreign surface, platelets, "globulin substance," and plasma proteolytic enzyme was studied and the results discussed.

The effect of the administration of the drug upon blood cytology, liver function, plasma proteins, especially fibrinogen, was studied and no significant abnormalities found.

Vitamin K (synthetic) was found not to act in any way as an antidote to the effect of administration of the drug.

Whole blood transfusion was found to have only a transitory effect or no effect upon the abnormal clotting mechanism in patients receiving the drug.

It is suggested that the variable effect of the drug upon blood coagulability, its prolonged action after discontinuation, and its difficulty in control render the drug a poor heparin substitute, and that great caution must be used in its administration.

AUTHORS.

Taylor, R. D., and Page, I. H.: The Effect of Antipressor Kidney Extract, Angiotonin, Methyl Guanidine and Tyramine on Cardiac Output as Measured by the Ballistocardiograph in Hypertensive and Normal Persons. Am. J. M. Sc. **205**: 66, 1943.

The cardiac effects of tyramine, and less so of methyl guanidine, as measured by the ballistocardiograph are such as to make it unlikely that they participate in the genesis of renal hypertension. On the contrary, angiontonin exhibits properties which are consonant with those anticipated from knowledge of the cardiodynamics in hypertension. This view is strengthened by the observation that antipressor,

angiotonin-destroying extracts of kidneys, administered to hypertensive patients, abolish at least one characteristic action of angiotonin, i.e., they increase the depressed cardiac output.

AUTHORS.

Zurrow, H., Saland, G., Klein, C., and Goldman, S.: The Effect of Testosterone Propionate in the Treatment of Arteriosclerosis Obliterans. J. Lab. & Clin. Med. **28**: 269, 1942.

Twenty-three patients suffering from obliterative vascular disease of the lower extremities were studied to note the effect of testosterone propionate on the signs and symptoms of their disease. Eight cases received biweekly intramuscular injections of 25 mg. of testosterone propionate; fifteen patients were observed as controls. The entire study was carried on over a period of eighteen months.

No significant effect was noted in the treated cases with respect to vascular anatomic status, tissue anatomic status, vascular reserve, claudication, rest, pain, or functional status, as compared with the control cases.

AUTHORS.

Goodman, J. I., Corsaro, J. F., and Stacy, R.: Mercurial and Xanthine Diuretics in Chronic Congestive Heart Failure: A Comparative Survey. Arch. Int. Med. **70**: 975, 1942.

It is proposed that accurate clinical methods for the evaluation of mercurial and xanthine diuretics in patients with hydropic cardiac disease require a preliminary period of treatment until all grossly visible edema has disappeared. This disappearance has been determined from the strict use of the daily weight of the patient, and the resultant condition has been called by us a "state of balance."

In patients in this "state of balance" only the really effective diuretics are capable of producing a further diuresis.

The following observations were made on sixteen patients given a total of 278 injections:

Injectable preparations in which mersalyl solution was combined with theophylline or theophylline with ethylenediamine were notably less efficient than pure mersalyl solution administered in similar doses.

Oral and rectal modes of therapy which employed combinations of mersalyl solution and theophylline produced little diuretic effect compared with that produced by injectable preparations administered to the same patients.

Theophylline with ethylenediamine (7½ grains) given intravenously to patients in a "state of balance" did not produce any evident diuresis by itself.

Finally, the greatest diuresis was produced by mersalyl solution (1 c.c.) given intramuscularly one hour after intravenous administration of theophylline with ethylenediamine (7½ grains). A superior degree of diuresis resulted, which was equalled only by a dose of mersalyl solution alone containing four times as much mercury, namely, 4 c.c.

AUTHORS.

Campbell, M.: Partial Heart Block Due to Digitalis. Brit. Heart J. **4**: 131, 1942.

Digitalis therapy is one of the commonest causes of partial heart block with dropped beats, and a common cause of a P-R interval that is much prolonged without dropped beats. Other factors, however, are generally present, and the most important of these seems to be some lengthening of the P-R interval before digitalis therapy; even then, a concurrent infection is often the immediate cause of the dropped beats.

In a series of cases of partial heart block nearly 40 per cent of those with dropped beats were being given digitalis, and 15 per cent of those with latent heart block.

The most essential prerequisite was some prolongation of the P-R interval before treatment. In those with partial heart block and dropped beats, and in those with latent heart block, it averaged 0.21 second. Only in three of twenty-three was the P-R interval below 0.18 second; in these three it was 0.16 second, and in two of them there was acute infection also. When there were no dropped beats, the P-R interval was on the average increased to 0.26 second. When there were dropped beats, there were most often two responses before the dropped beat, and the lengthening P-R intervals averaged 0.22 second, 0.37 second, dropped beat, etc. This, however, was the average of very varied figures, which averaged 0.22, 0.29, dropped beat, etc.; in three, and 0.22, 0.41, dropped beat, etc., in six patients. No special difference could be found between the groups with these different responses. Apart from the presence of latent heart block the etiology of the underlying heart disease did not seem of importance, though, naturally, congestive failure was present in the majority, as this was usually the indication for digitalis.

The presence of a concurrent infection seemed the next most important factor. When there were dropped beats, more than half had some active infection at the time. Sometimes this was a severe infection such as active rheumatic carditis, but often it seemed of a trivial nature, and it was only because digitalis could be taken at other times without producing dropped beats, or because the rise of temperature ran so closely parallel to their onset, that one could be sure of the connection. When there was latent heart block, an active infection was less often present, but was noted as the cause in a few cases. In others where there was no infection but a heart that was very seriously damaged (as shown by the patient's death within a relatively short time), this seemed an additional factor, making the conduction time more sensitive to digitalis than usual.

Large amounts of digitalis were rarely the cause. Three of these cases were taking amounts that would generally be thought excessive (and curiously enough two of these had acute infections at the time, and there seemed no reason why any digitalis should have been given); seven had amounts that were large, but quite reasonable; and twenty-two were taking amounts that were average or sometimes even small.

In general, there seemed to be no severe ill effects, even when there were dropped beats; and the block passed off quickly (within two or three days), but, of course, this immunity is dependent on the heart block being recognized quickly.

There seems no reason why the chance finding of latent heart block should prevent adequate treatment with digitalis where this is indicated, though naturally the case should be watched even more carefully than usual.

AUTHORS.

Shleser, I. H., and Asher, R.: Efficacy of Adrenal Cortical Extract and of Paredrine in the Prevention of Experimental Shock Following Venous Occlusion of a Limb. Am. J. Physiol. **138**: 1, 1942.

Adrenal cortical extract (ACE) is a beneficial therapeutic agent in the treatment of shock following venous occlusion of a limb.

ACE shows a definite tendency to reduce the amount of fluid lost into the edematous limb, an action more striking than that of desoxycorticosterone acetate (DCA) alone. However, it has a less marked effect on survival than DCA.

Paredrine, a vasopressor substance, is of no benefit in shock in which the initiating factor is an escape of plasma fluid, since it appears to augment the escape of fluid through capillaries with impaired permeability.

AUTHOR.

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Erratum

The two illustrations reprinted here were printed upside down on page 578 of the May issue, in the article by Murnaghan, McGinn, and White, "Pulmonary Embolism With and Without Acute Cor Pulmonale, With Especial Reference to the Electrocardiogram."

Please paste these correctly placed figures over those on page 578.

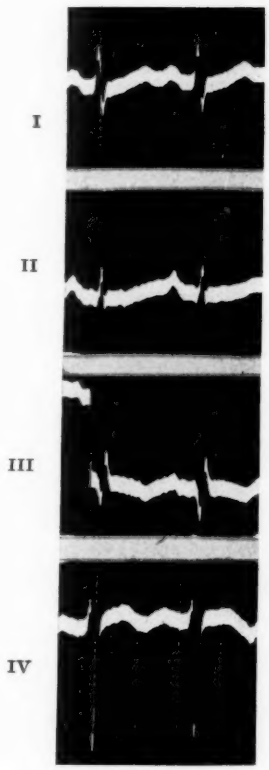

Fig. 2.

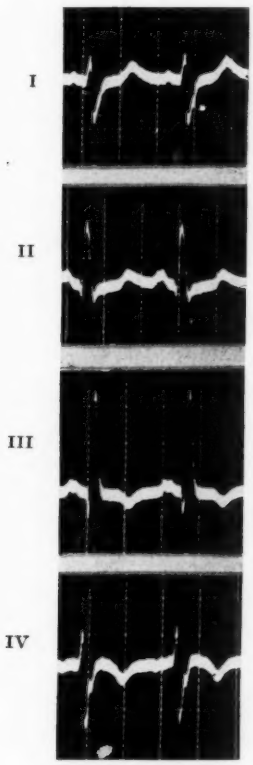

Fig. 3.

Fig. 2.—Case 2, W. R. August 17, 1939, 24 hours after most recent attack.
Fig. 3.—Case 3, F. B. April 24, 1941, 20 hours after first attack, 12 hours after second attack.

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*An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

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